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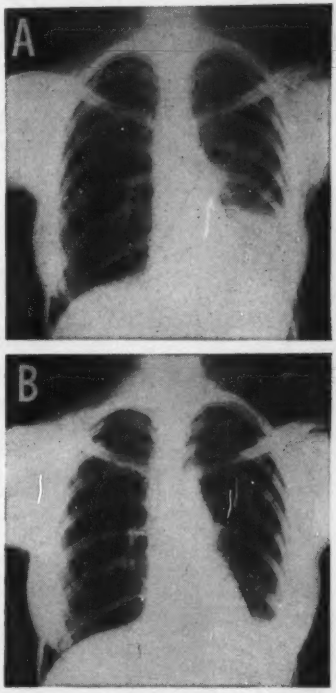

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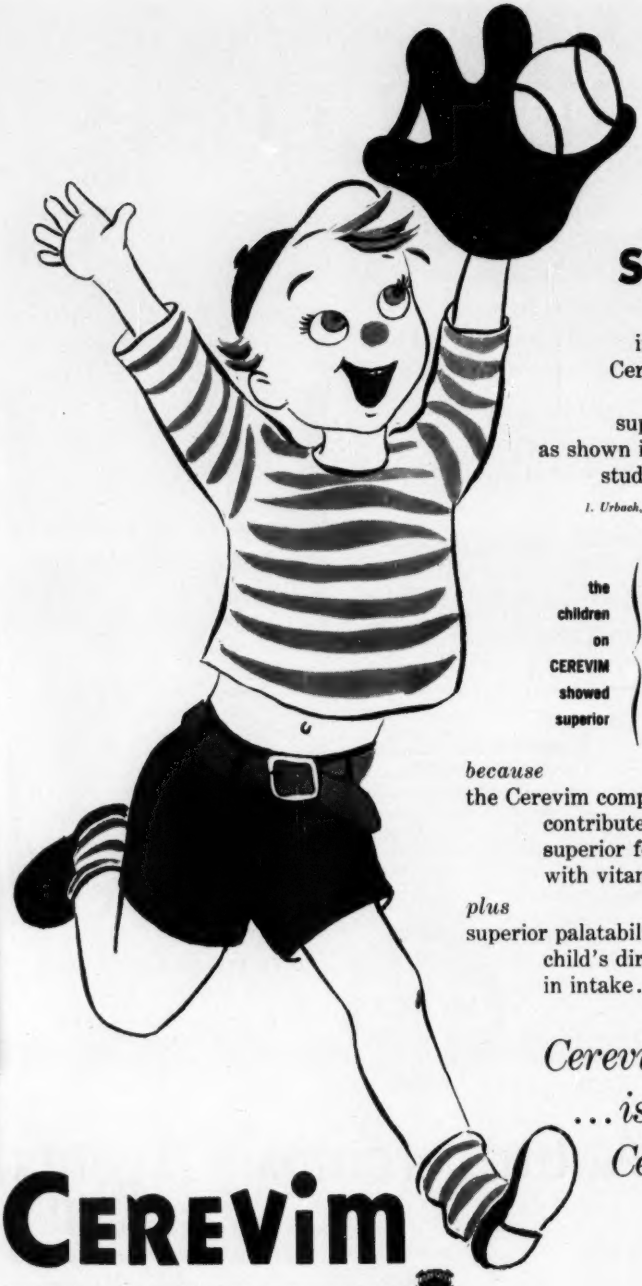

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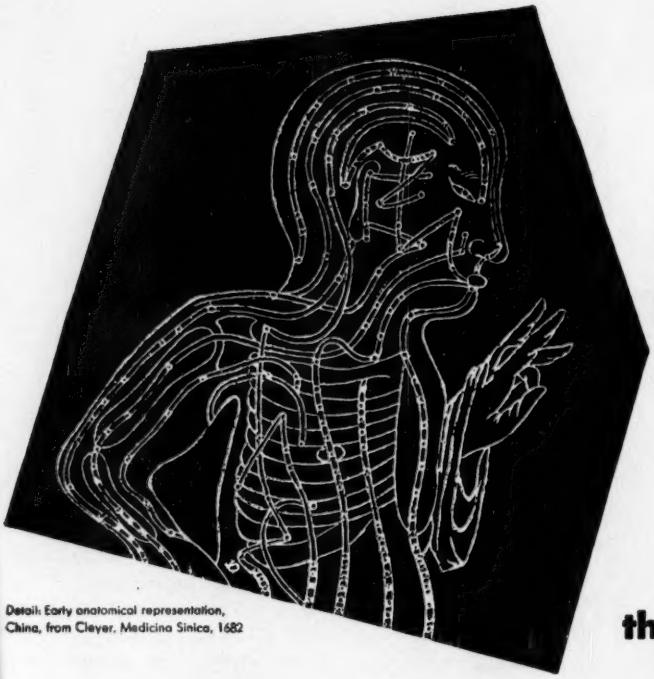

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1. Krasno, L., and Rhoads, P. (1949), The Inhalation of Penicillin Dust; Its Proper Role in the Management of Respiratory Infections, Amer. Prac., 11:649, July.

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PRECOCIOUS SEXUAL AND SOMATIC DEVELOPMENT IN BOYS DUE TO CONSTITUTIONAL AND ENDOCRINE FACTORS

W. W. ENGSTROM, M.D.
MILWAUKEE
AND
PAUL L. MUNSON, D.D.S.
BOSTON

THE SOMATIC and sexual development of a person from infancy to adulthood consists in a series of transitions. The age at which certain phenomena of maturity usually make their appearance has been established for normal rates of development. However, it is recognized that considerable variation in the degree of development and time of appearance of these phenomena occurs in apparently normal persons. Occasionally, the time of appearance of certain of the manifestations of maturity may be so retarded or accelerated that the development of the person must be considered as distinctly abnormal. This report is concerned with pathological precocity, not with physiological "early" sexual development.

Discussions of the different causes of precocious development have been well presented by different authors [1]; therefore problems in differential diagnosis will not be considered. This report concerns the clinical and laboratory findings exhibited by two brothers with precocious sexual and somatic development. Another brother, intermediate in age, has shown no developmental abnormality. The fact that the father of these boys gave a history of a similarly abnormal developmental pattern provides further interest and implicates a genetic or constitutional factor as the fundamental cause of the anomaly. With present knowledge the term "constitutional" precocious development appears to be justifiable and applicable to these cases. It has been applied to describe pathological precocity in boys or girls for which no tangible cause has been found and in whom a premature awakening of some phases of maturation, especially in gonadal and somatic growth, occurs. A

This work was aided by a grant from the Office of Naval Research.

From the Department of Internal Medicine and the Department of Pharmacology, Yale University School of Medicine, New Haven, Conn.

The present address of Dr. Engstrom is Department of Internal Medicine, Marquette University School of Medicine; that of Dr. Munson, Department of Dental Medicine, Harvard Medical School.

1. (*a*) Wilkins, L.: Abnormalities and Variations of Sexual Development During Childhood and Adolescence, Advances Pediat. **3**:159, 1948. (*b*) Seckel, H. P. G.: Precocious Sexual Development in Children, M. Clin. North America **30**:183-209 (Jan.) 1946. (*c*) Weinberger, L. M., and Grant, F. C.: Precocious Puberty and Tumors of the Hypothalamus: Report of a Case and Review of the Literature, with a Pathophysiologic Explanation of the Precocious Sexual Syndrome, Arch. Int. Med. **67**:762-792 (April) 1941. (*d*) Gross, R. E.: Neoplasms Producing Endocrine Disturbances in Childhood, Am. J. Dis. Child. **59**:579-628 (March) 1940.

few reports of isolated cases of this type in boys are available.[2] However, in only four reports has this disorder appeared to be familial, thus making its genetic nature more certain. In 1852 Stone [3] first described the condition in a father and son; Orel,[4] in 1927, in two brothers; Rush,[5] in 1937, in a father and two sons and several other male relatives, and Sigrist,[6] in 1940, in two brothers. This, then, is the fifth such reported instance.

For comparison, a boy with good evidences of adrenal cortex hyperactivity will be presented. When Wilkins [1a] reviewed this problem in 1948, he pointed out that "adrenal cortical hyperplasia" coming on after birth but before 10 years of age and causing either the adrenogenital syndrome or Cushing's syndrome had not been reported in boys. The patient to be discussed first showed evidences of precocious sexual and somatic growth (adrenogenital syndrome) at 3½ years of age and at 6 years exhibited a remarkable picture of accelerated development.

In the discussion a comparison will be made between the maturity phenomena that ordinarily occur in normal puberty and the sequence of these developments which was exhibited by these boys with precocious growth.

MATERIALS AND METHODS

Clinical and laboratory data were obtained on W. S. Sr., the father, and on R. S. and P. S., the two sons with constitutional precocious development. Patient W. S. Jr., another son, showed no developmental abnormality. Similar data were obtained on another patient, T. J. S., who at 6 years of age showed clinical and laboratory evidences of adrenal cortex hyperactivity. The urinary 17-ketosteroids were determined by the method of Holtorff and Koch [7] with the slight modifications introduced by Pincus and Pearlman [8] and Nathanson and Wilson.[9] The alpha and beta fractions of the total neutral 17-ketosteroids were determined by the method of Talbot [10] as modified by Mason.[11] The urinary gonadotropins (follicle-stimulating hormone) were determined by the method of Varney and Koch.[12]

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REPORT OF CASES

The histories, clinical findings and laboratory data on these cases follow.

R. S. was born on Nov. 10, 1941. His birth weight was 6 pounds 9 ounces (2,950 Gm.); height, 20 inches (51 cm.), and chest and head circumferences, 12 and 13 inches (30 and 33 cm.) respectively. He appeared to be a normal boy. He gained weight steadily, weighing 20 pounds (9,072 Gm.) at 6 months and 25 pounds (11,340 Gm.) at 1 year. He sat unsupported at about 6 months and walked at 15 months. He was seen by the family pediatrician at 1 year, and it was felt that he was a normal child. However, at about 18 months of age he began to grow rapidly, the penis and scrotum were noted to be abnormally large and shortly thereafter pubic hair began to appear. Some of the pertinent features of his developmental pattern are given in the table. He had had no antecedent illnesses. His parents noted that his personality became more forceful and assertive and that he had a rather violent temper. In July 1943 (chronologic age, 20 months)

Course of Development and Hormone Excretions of the Two Boys with Constitutional Genital Precocity and of the Boy with Adrenal Cortical Hyperactivity

Maturity Phenomena, Appearance of Patient	"Constitutional" Precocious Development Age, Yr.		"Adrenogenital" Syndrome Age, Yr.
	R. S.	P. S.	T. J. S.
Onset of disorder	1½	2½	3¾
Maximum growth (height)	1½ to 3½	2½ to 4½±	3¾ to 5¾±
Maximum testicular growth	1½ to 3½	2½ to 4 2/12±	0
Maximum penile growth	1½ to 3½	2½ to 4 2/12±	3¾ to —
Beginning pubic hair	1½	2½	4±
Adult type pubic hear (group 5) *	3½	4 2/12	0 at 6½
Axillary hair	8±	0 at 5 4/12	0 at 6½
Facial hair	8±	0 at 5 4/12	0 at 6½
Adult type voice	3½	4 2/12	Incomplete at 6½

	R. S.		P. S.		T. J. S.	
	Age, Yr.	Mg./ 24 Hr.	Age, Yr.	Mg./ 24 Hr.	Age, Yr.	Mg./ 24 Hr.
17-Ketosteroid excretion	6 2/12	1.6	4 7/12	2.3	5¾	37 and 31
	6 3/12	2.4	4 9/12	2.3	5 11/12	32.7
	7 7/12	4.3			6½	40.0 and 53.2 (10% β-steroids)
Gonadotropin excretion	7 11/12	<5 M. U.	4 9/12	<5 M. U.		

* Greulich and others [18] classified the successive stages into "maturity groups" in the transition from physical immaturity to the degree of maturity which is associated with late adolescence. In his "maturity group 5" pubic hair is typically adult in quantity and in type.

he was admitted to the hospital. He did not appear ill. At this time there was no axillary or facial hair, no acne, no voice change and no gynecomastia. The fontanels were closed. Blood pressure was 110 mm. Hg systolic and 70 mm. diastolic. The penis was large, measuring 6 cm. in length and 2 cm. in diameter in partial erection. The scrotum was enlarged and the skin wrinkled; the testes were firm in consistency and larger than would be anticipated for his age. There was a fairly dense growth of dark, crisp pubic hair. The results of a complete neurological examination were unremarkable. At the Child Development Clinic it was felt that the patient had borderline retarded mental development, having a maturity level of 15 months (chronologic age, 20 months). Clinically there was nothing definite to suggest an intracranial lesion except for the slight mental retardation.

The patient had negative Kahn, tuberculin and Schick reactions. The blood cell count and results of urinalysis were unremarkable. The value for serum sodium was 140.3, for potassium 4.8, for bicarbonate 20.8 and for chloride 103.6 milliequivalents per liter; for albumin 4.8 and for globulin 2.7 Gm. per 100 cc. The results of a spinal fluid examination were unremarkable. A roentgenogram of the skull showed it to be normal. A pneumoencephalogram revealed no evidence of tumor, although the ventricles seemed slightly enlarged and there was poor filling of the

subarachnoid space on the right. Intravenous pyelograms showed the kidneys in normal position and no evidence of suprarenal mass. Roentgenograms of the wrists revealed a bone age of approximately 3 years. The bones were unusually large, with marked thickening of the cortex and heavy widened zones of provisional calcification of cartilage at the epiphysial lines of growth. Since there was no clearcut evidence of adrenal cortex disease or of a lesion of the central nervous system, the patient was discharged from the hospital.

In November he was seen in the clinic, where deepening of the voice was noted as well as further growth of the genital organs and of pubic hair. Speech development was definitely retarded.

In June 1944, at an age of 31 months, it was found in the Child Development Clinic that his motor behavior was appropriate to 36 months of age, his personal-social maturity to 28 months and his vocabulary and use of language to 15 months. It was apparent that his mental development was not consistent with any one age.

The patient was not seen again until July 1945 (chronologic age, 3 years 8 months), at which time the penis, scrotum and testes were of adult size. There was a heavy growth of

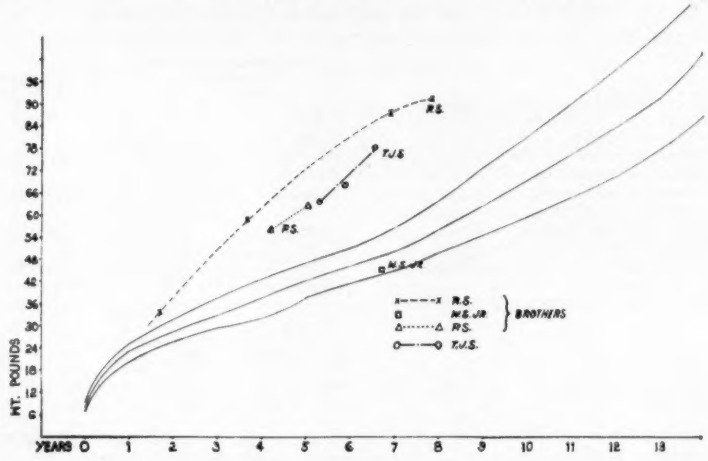

Fig. 1.—The solid lines, taken from the growth charts of Jackson and Kelly (Growth Charts for Use in Pediatric Practice, J. Pediat. **27**:215-229 [Sept.] 1945), represent normal growth in height in boys according to their chronologic ages. The middle curve gives the mean height; the outside curves represent patients on the height scale that are 1 standard deviation above the average and 1 standard deviation below the average. Available data on the heights of the three brothers, *R. S.* and *P. S.* (who were precociously developed) and *W. S. Jr.* (who was normal), are given, as well as those for patient *T. J. S.* (with adrenogenital syndrome).

pigmented, curly adult type pubic hair that extended on to the inguinal areas but did not extend to the umbilicus. However, no axillary or facial hair had appeared, and the body hair was not unusual. The voice was now very deep, being that of a male adult. The general body structure was that of a boy-sized man; the overgrowth appeared to be generally symmetrical. Another skull film showed the skull to be normal, and films of the wrists and ankles revealed a bone age of 13 years. The slight mental retardation was still apparent. In August both adrenal areas were explored but no tumor was found and no definite adrenal enlargement was noted at operation. No biopsy specimen was obtained. The patient had an uneventful convalescence.

The patient was seen again in January 1948, at a chronologic age of 6 years 2 months. His physical examination revealed no significant change from the previous examination except for further increase in growth in height and weight (figs. 1 and 2). His height was 53.4 inches (136 cm.) and span 53 inches (135 cm.). The first molar teeth had erupted, but the deciduous incisor teeth were still present. The genital organs were of adult size and the voice was deep, but he had no acne, axillary hair or excess facial hair. Roentgenograms of the wrist revealed a

bone age of 15 years. The serum precipitable iodine was normal, being 5.2 micrograms per 100 cc. (3.8 to 7.8 micrograms per 100 cc. for normal adults). Assays of the urine for 17-ketosteroids and gonadotropin are given in the table.

By 7 years of age the permanent upper and lower middle and lateral incisor teeth had erupted. Some facial acne was present. Axillary and facial hair had still not appeared. At 7 years and 5 months a photograph of the patient and his brothers was obtained (fig. 3). There had been no unusual behavior problems at school, although at home he was not always easy to manage, having occasional temper tantrums.

When last seen, at 8 years of age, a very small amount of axillary hair had appeared and there were some long, soft, dark hairs on the upper lip. By this time there seemed to be evidence of a tapering off in the increments in weight (fig. 2) though not in height (fig. 1). Although the sexual organs seemed mature, he had shown no sexually aggressive trends, no masturbatory tendencies or nocturnal emissions. He was emotionally boyish, enjoyed the usual games of childhood and got along well with his classmates. However, his school work was below average.

W. S. Jr., the normal child, was born in March 1943. By 6½ years of age his rate of growth was within the range of normal (figs. 1 and 2). The results of his physical examination were

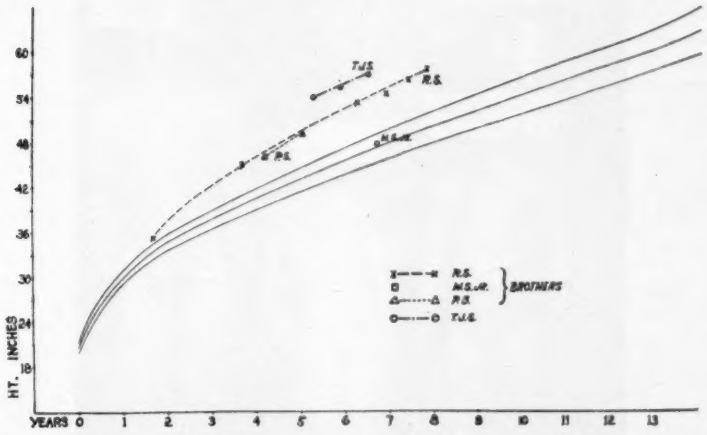

Fig. 2.—The solid lines, taken from the growth charts of Jackson and Kelley (Growth Charts for Use in Pediatric Practice, J. Pediat. **27**:215-299 [Sept.] 1945) represent normal gains in weight in boys according to their chronologic ages. Since the weight curve is slightly skewed for age groups, the middle curve represents the median (fiftieth percentile) weight; the outside curves represent the eighty-fourth and sixteenth percentiles. Data on the weights of the three brothers, *R. S.* and *P. S.* (who were precociously developed) and *W. S. Jr.* (who was normal), are given, as well as those for patient *T. J. S.* (with adrenogenital syndrome).

entirely unremarkable (fig. 3). Although he seemed to learn little faster than his brothers, he was less of a problem in management to his parents.

P. S. was born in September 1944, weighing 3,290 Gm. and measuring 20½ inches (52 cm.) at birth. On the third day of life diarrhea developed with small amounts of bright red blood in the stools. The results of the physical examination were unremarkable, and the blood count, prothrombin time and bleeding and clotting times were within the limits of normal. He did not vomit or show signs of dehydration or acidosis. The qualitative composition of his formula was changed on the sixth day, and shortly thereafter the diarrhea ceased and he began to gain weight. No completely satisfactory reason was found for the diarrhea. In any event, he had no further similar difficulty. The patient was then not seen by any physician until he was examined at our request in November 1948. Pertinent data on his pattern of growth are given in the table.

At this time (chronologic age 4 years 2 months) his parents stated that he had appeared to be a healthy, normal infant. He had had none of the childhood illnesses. He sat alone at 6

months and at 13 months walked and said a few words. He had an excellent appetite and experienced no episodes of weakness, vomiting or diarrhea. He had had no headaches or other complaints. At about 2½ years of age the parents noted beginning precocious genital development accompanied with accelerated somatic growth, the appearance of some pubic hair and deepening of the voice. Thus, the first evidences of precocious development appeared about one year later than in his oldest brother, R. S. Rapid growth continued so that the patient soon outstripped his older, normal brother (W. S. Jr.) in height, weight and strength. Mild stimulation of the genitals, such as removing his trousers, caused an unsustained penile erection; however, on no occasion were emissions noted by the parents. There had been no unusual attraction to the

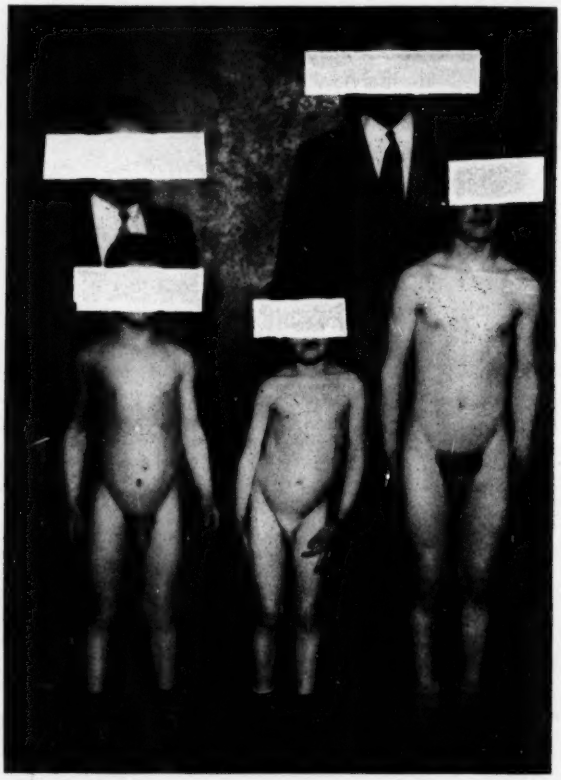

Fig. 3.—Photograph of the three brothers: left to right, P. S. at 4 7/12 years of age, W. S. Jr. at 6 1/12 years and R. S. at 7 5/12 years. The father of these boys is at the left; a normal, 6 foot man is at the right.

opposite sex. His behavior was usually docile and entirely boyish, but when angered he had a moderately violent temper.

On examination (age 4 years 2 months) he presented a remarkable picture of precocious genital and somatic development. His height was 46.1 inches (117 cm.); span, 44.2 inches (112 cm.), and weight, 56½ pounds (25,628 Gm.) (figs. 1 and 2 contain further data on subsequent growth). He was unusually muscular, his voice was deep and there was a moderate amount of dark, crisp, adult type pubic hair which extended to the inguinal areas. There was no acne or evident excess of facial or body hair. No axillary hair was present. The penis was 6.5

cm. in length, and each testis measured about 3 by 2.5 cm.; the testes were firm and smooth and almost resembled those of a normal adult. The prostate was easily felt. Visual fields were normal. The fundi were unremarkable. The results of the neurological examination were normal. None of the permanent teeth had erupted. Examination of the heart, lungs and abdomen revealed no abnormality. The blood pressure was 108 mm. Hg systolic and 68 mm. diastolic.

A roentgenogram of the skull showed it to be unremarkable except that the skull was larger than would be expected for his chronologic age. Films of the hands and wrists revealed the presence of all the carpal centers of ossification. Normally, not all are well seen until 13 years of age. Likewise, all the centers of ossification of the metacarpals and phalanges were well developed. Films of the elbows showed the presence of all the centers of ossification of the humerus, radius and ulna. The medial epicondylar center was well developed; usually this does not appear until 14 years of age. Data on the urinary 17-ketosteroids and gonadotropin excretions are given in the table.

When last seen, at 5 years and 4 months of age, the patient was still growing rapidly. At this time, the genital organs appeared to be of normal adult size. No acne and no axillary or facial hair had yet appeared. The first permanent molar teeth and one permanent incisor tooth had erupted. His personality and emotions had remained unchanged.

W. S. Sr., the father of the above three boys, was of Yankee-American stock. He was unaware of any unusual pattern of growth or development in any other member of his immediate family. His father and only brother were of average height, measuring about 5 feet 9 inches (175 cm.). The patient stated that at about 6 or 7 years of age his voice became deep and genital growth and pubic hair appeared. Concurrently, there was rapid growth in height and strength. He remembered this clearly because while in grammar school he was teased by his classmates about his large genitals and unusually rapid growth. He recalled that he was taller and stronger than his classmates until about 11 years of age, when he stopped growing and was soon outstripped in height by his contemporaries. The patient did not recall that he was unusually aggressive, physically or sexually. In fact, he considered himself to be rather shy. He did not become seriously attracted to the opposite sex until his late teens and did not have intercourse until 22 years of age.

When seen here he appeared to be a normal, well developed, short man of 37 years of age. His height was 5 feet 1⅝ inches (157 cm.); weight, 133 pounds (60.330 Kg.), and span, 5 feet 0 inches (152 cm.). The results of the general examination were unremarkable. A 24 hour specimen of urine revealed 8.6 mg. of 17-ketosteroids.

T. J. S. was born in January 1943; his birth weight was 7 pounds 8 ounces (3,402 Gm.). He thrived as an infant and had no episodes of weakness or gastrointestinal upset. He sat with support at about 4 months, walked at 1 year and said words at 18 months and sentences at 2 years. His mother and father were healthy. In the fall of 1946, at an age of 3 years 9 months, it was first noted that the patient was growing abnormally rapidly and that his appetite had increased. Pertinent data on his development are outlined in the table. Soon thereafter pubic hair began to appear, his voice deepened, masturbatory trends were noted and he developed a fetish behavior of wearing his mother's nightgown to bed. On a few occasions he even stole women's underwear from the neighbor's clothes line. However, he seemed to do well in school; he was a fairly good student and played well with other children. In April 1948, at 5 years 3 months of age he was hospitalized at another hospital, where examination revealed some growth of pubic hair, a deepened voice and an enlarged penis. He was 54 inches (137 cm.) in height and weighed 64 pounds (29 Kg.). A roentgenogram of the skull showed it to be normal and the results of intravenous pyelograms were unremarkable. The results of a glucose tolerance test were reported as normal. Two 24 hour urine collections revealed 37 and 31 mg. of 17-ketosteroids.

He was discharged from this hospital and entered New Haven Hospital, in December 1948, at 5 years 11 months of age. His past history revealed the above findings, but, in addition, the parents stated that at 2 years of age the patient sustained a "bad fall" and shortly thereafter a mild right internal strabismus developed. An attempt at surgical repair of the defect failed.

The patient was cooperative and appeared healthy. The systolic blood pressure was 120 mm. Hg; diastolic, 80 mm. He was large for his age (figs. 1 and 2), weighing 67½ pounds (30.6 Kg.) and measuring 55 inches (140 cm.) in height. Growth seemed to be increased in all

dimensions. The ophthalmologist found that the pupils were of equal size when exposed to bright light, the fundi were unremarkable and there was a mild right internal strabismus which corrected itself when the other eye was covered. It was his opinion that this residual alternating esophoria was unrelated to the general clinical syndrome. Unfortunately, no accurate record was made of the patient's dental age. The heart, lungs and abdomen were normal. The penis was enlarged, approaching adult size, but the testes were preadolescent in size (fig. 4). The presence of an enlarged penis with small testicles has been termed "dissociate virilism" and provides strong clinical evidence of a nongonadal source of the disorder. There was a moderate growth of dark, crisp pubic hair about the base of the penis, but no axillary or facial hair was noted. The results of the neurological examination were unremarkable.

Laboratory studies revealed that the serologic reactions of the blood were negative and the blood count and urinalysis were normal. The value for serum chloride was 100, for bicarbonate 23.7, for sodium 138.3 and for potassium 4.6 milliequivalents per liter; the nonprotein nitrogen was 27 and the fasting blood sugar 76 mg. per 100 cc. A lumbar puncture revealed a normal spinal fluid. An electroencephalogram was normal. The urinary 17-ketosteroid excretion

Fig. 4.—Photograph of the genitals of T. J. S. at 5 11/12 years of age showing the enlarged penis, moderate growth of dark hair about the base of the penis and the relatively small testicles.

was 32.7 mg. per 24 hour period. Intravenous pyelograms were normal. Roentgen examinations of the bones revealed a bone age of about 15 years.

The patient was discharged from the hospital and readmitted in July 1949 (chronologic age, 6½ years). Except for evidences of further rapid growth, the physical findings were unchanged. The 17-ketosteroid excretion was still markedly elevated, being 40.0 mg. and 53.2 mg. per 24 hour period in two different collections. Fractionation of the latter extract into the 3-hydroxy-alpha and 3-hydroxy-beta fractions revealed 47.6 mg. of "alpha" steroids and 5.6 mg. of "beta" steroids (10 per cent of the total).

Because of the strong evidences of adrenal cortex overactivity and because the possibility of an adrenal cortical neoplasm could not be excluded, both adrenal areas were explored on August 5 by Dr. Max Taffel. At operation the right adrenal gland appeared to be of normal size, shape and consistency; the left was probably about twice normal size but was otherwise not unusual. There was no evidence of neoplasia. Whether the combined weight of the adrenals was much increased over normal it is impossible to say. A biopsy specimen was taken from the left adrenal. The specimen was examined by Dr. H. S. N. Greene, who reported: "The slide shows an excellent section through the adrenal which demonstrates the three zones of the cortex. There is no outstanding pathological process apparent on examination of the specimen; however, the

depth of the reticular layer appears to be increased. However, there is no pathological change noted, and the cells are arranged as usual in anastomosing cords. Diagnosis: hyperplasia of the reticulous zone, compatible with adrenogenital syndrome." The patient was discharged from the hospital after an uneventful convalescence and has not been seen since.

COMMENT

Two brothers, R. S., and P. S., have been presented with greatly accelerated development which was most probably due to precocious growth and function of the gonads. Since the father also presented a similar history, it seems reasonable to consider the phenomenon a familial trait, genetically or constitutionally determined. Another boy, T. J. S., unrelated to the above family, was also precociously developed but exhibited no clinical evidence of gonadal stimulation; rather he showed evidences of adrenal cortical overactivity. It is pertinent to consider these two pathological processes, as they affect gross abnormalities of growth and other maturity phenomena.

The marked deviation exhibited by these patients from normal rates of growth in height and weight is clear from figures 1 and 2. The boys with constitutional gonadal precocity (R. S. and P. S.) were more stockily built than was T. J. S., as evidenced by their greater relative weight-height development. However, T. J. S. was gaining weight rapidly when last seen. With such limited data it is, of course, impossible to determine the significance of this finding.

Since R. S. was followed from the inception of his disorder, examination of his growth pattern in comparison with other maturity phenomena will be considered. In normal boys, after 2 years of age increments in average height, year by year, diminish slightly until about 11 years of age, at which time a spurt (acceleration) in annual increments of stature occurs.[13] This period of accelerated growth lasts on an average for about three years, i. e., until 14 years; thereafter, rapid deceleration in growth increments occurs. In any individual, however, this period of accelerated growth is usually shorter, being about two years in duration.[14] Increments for average weight by years assume a slightly different picture. After 2 years of age and until 9 years, there is a progressive, small increase in increments of weight year by year; thereafter, the acceleration becomes rapider, and this acceleration in yearly weight increments ends at approximately the same time as does that for height, i. e., at about 14 years of age. Thus, the period for rapid acceleration in weight is considerably longer than that for height. With this information concerning normal growth, it is interesting that R. S. showed the greatest increments in height (fig. 1) for about two years (from 1½ to 3½ years of age), i. e., for an interval quite like that for the normal "spurt" in height for normal boys. After this time his growth curve assumed a direction which has been approximately parallel with the curves for normal growth. Further, it is apparent from figure 2 that the period for rapid acceleration in weight was spread out over

13. Simmons, K.: The Brush Foundation Study of Child Growth and Development: II. Physical Growth and Development, Monographs of the Society for Research in Child Development, vol. 9, no. 1, (serial no. 37), Washington, D. C., Society for Research in Child Development, Nat. Res. Council, 1944.

14. Stuart, H. C.: Normal Growth and Development During Adolescence, New England J. Med. **234**:666-672 (May) 1946.

a longer period, though greatest during the time of most rapid gain in height. Thus, the general picture of growth in height and weight in R. S. was like the adolescent "spurt" of normal boys except that it occurred at an abnormally early age. Although no data are available for P. S. and T. J. S. during the inception of their disturbed growth rates, it is likely that they showed a pattern quite similar to that of R. S., especially since their growth curves (particularly for height) are now running parallel to the normal curves and to that of R. S. These findings support the thesis that tissues (in this case the skeletal and probably the muscular system) respond in a fundamentally uniform manner whether stimulated to increased growth by normal or by abnormal influences. The pattern of response appears to be an inherent birthright of the tissues stimulated.

Although R. S. will have to be followed for a longer period, it appears from his weight curve that deceleration in growth is beginning at about 8 years of age. Normally, this is not seen until 14 or 15 years of age. If deceleration in his growth is beginning, it will argue for an ultimately short stature, possibly comparable to that of his father. Also, from the photograph and from a comparison of standing height to arm span measurements it is clear that there was a rather general macrosomia, a harmonious overgrowth of the skeletal and muscular systems.

In normal boys other characteristics help to identify the period of maximal increments of growth (especially of height). A comparison was made of the time of appearance of certain maturity phenomena in R. S. and in normal boys. While considerable difference exists in the chronologic ages at which the manifestations of maturity appear in different normal boys, the sequence in the appearance of these manifestations is very consistent. Normally, with the onset of maximal linear growth there occurs rapid development of the primary sexual organs (testes, penis, epididymis and prostate). In R. S., whose period of maximal growth was between 1½ and 3½ years, the penis and testes grew rapidly in size. Normally, the secondary sexual characters (pubic, axillary and facial hair and a deepened voice) appear at different intervals after the rapid growth of the primary organs begins. According to the extensive studies of Greulich and his associates,[15] pubic hair appears shortly after accelerated growth of the testis begins and boys will have a full mature growth of pubic hair but with a horizontal distribution with deceleration of testicular growth. Axillary hair appears only several months after the pubic hair appears but while the latter is still localized about the base of the penis. Facial hair normally appears after considerable axillary hair is present. A deepened voice is an even later development, normally occurring at about 15 years of age.

In R. S. maximal pubic hair growth developed as would be expected during maximal development of the testes and during maximal increments in height. By July 1945, (age 3 years 8 months) penis, scrotum and testes were of adult size and there was a good growth of adult type pubic hair. This stage of genital development and pubic hair growth would place R. S. well in Greulich's [15] "maturity group 5," the most advanced stage of development before completely

15. Greulich, W. W.; Dorfman, R. I.; Catchpole, H. R.; Solomon, C. I., and Culotta, C. S.: Somatic and Endocrine Studies of Puberal and Adolescent Boys, Monographs of the Society for Research in Child Development, vol. 7, no. 3, (serial no. 33) Washington, D. C., Nat. Res. Council, 1942.

adult characteristics are attained. Further, according to Greulich's studies, the development of the skeleton tends to keep pace with that of the various external characters on which the maturity groups are based. At a "maturity group 5" level, irrespective of chronologic age, a mean skeletal age of about 16 years would be expected. At this time R. S. had a skeletal age of 13 years. That his greatly advanced skeletal age had not quite kept pace with that expected from his maturity level is not surprising, since Greulich further showed that "within the same maturity group, boys who are older chronologically tend on the average to be more mature skeletally than the younger boys." Thus, the skeletal age of R. S. probably is not much different from what would be expected considering his chronologic age and maturity level.

Thus, in R. S., whose abnormality in growth appears to be due to precocious gonadal development, there was a relatively harmonious accelerated development, similar to that seen in normal boys, of the primary sex organs, pubic hair and the skeleton concomitant with the period of accelerated increments of growth in height and weight so that at a chronologic age of 3 years and 8 months he had, by these criteria, an average biologic age of about 14 years. Interestingly, however, harmonious acceleration in other features of maturity phenomena was lacking. His 17-ketosteroid excretion was only slightly greater than normal for his chronologic age; he showed no growth of axillary, facial or body hair until several years later (about 8 years of age); his dentition was not definitely accelerated, and he exhibited no pubescent personality, mentality or psychosexual behavior. These discrepancies will be briefly discussed.

At chronologic ages of 6 years 2 months, 6 years 3 months and 7 years 7 months, considerably after the maximal increments of growth had occurred, the 17-ketosteroid excretions a day of R. S. were only 1.6 mg., 2.4 mg. and 4.3 mg., respectively. Normal boys at comparable ages probably do not excrete more than 1.4 mg.[16] although Raices and Rivara [17] put the upper limit for 7 year old boys at 3.7 mg. Similarly, the precociously developed brother, P. S., did not excrete more than 3.0 mg. per 24 hour period. In any event, the 17-ketosteroid output of R. S. was not much above normal for his chronologic age. Biologically, however, at least according to his skeletal age and genital development he was about 14 to 15 years of age. The mean 24 hour excretion of 17-ketosteroids for normal 15 year old boys has been reported at 6.9 mg.,[18] 6.3 mg.[16] and 14.1 mg.[17] Since normal boys and girls excrete a similar and increasing amount of 17-ketosteroids up to the age of puberty and since the testes and the adrenal cortex are the only known sources of the urinary 17-ketosteroids, it has been felt that the adrenal gland is the chief source of these substances in normal childhood. In R. S. and P. S., however, it is possible that the slight increase in the 17-ketosteroids was mainly contributed by the testes. In any event, if these urinary steroids can reflect certain aspects of adrenal

16. Talbot, N. B.; Butler, A. M.; Berman, R. A.; Rodriquez, P. M., and MacLachlan, E. A.: Excretion of 17-Ketosteroids by Normal and by Abnormal Children, Am. J. Dis. Child. **65**:364-375, 1943.

17. Raices, A. E., and Rivara, L. T.: La eliminación de 17-cetoesteroides en niños, Semana méd. **1**:856-859 (June 19) 1947.

18. Miller, S., and Mason, H. L.: The Excretion of 17-Ketosteroids by Diabetics, J. Clin. Endocrinol. **5**:220-225 (May-June) 1945.

function, it would seem that in R. S. and P. S. these activities did not keep pace with their biologic age. Some workers [19] have suggested that as a person changes from a child to an adult, the fact that the urinary 17-ketosteroids rise implies a relation between the secretory activity of the adrenal and growth and development, and they have pointed out that correlation which exists between 17-ketosteroid excretion and urinary creatinine excretion and between 17-ketosteroid excretion and physical and skeletal maturity. The present study would raise some question as to whether or not the secretory activity of the adrenal cortex would necessarily condition the extent of growth and development. Even in normal adolescence the level of 17-ketosteroid excretion and extent of physical maturity may be, in part at least, only coincidentally correlated. Without knowledge of the influence of age and maturation on the intermediary metabolism of precursor hormones and without precise knowledge regarding which adrenal steroids give rise to these urinary steroids and what the biologic action of these precursors might be, it is possible only to speculate on the significance of the correlations between 17-ketosteroid excretion and observed maturity phenomena.

However, it is interesting that R. S. did not develop axillary or facial hair until about 8 years of age, in spite of the fact that genital maturity, adult type pubic hair and accelerated somatic and skeletal growth had existed for at least four years. The appearance of axillary hair was also "delayed" in P. S. It has been suggested by Albright [20] that "axillary and pubic hair are due to adrenal cortical function" and by Kepler, Peters and Mason [21] that "in women, and to a lesser extent in men, growth of pubic and axillary hair reflects adrenal cortical activity." On the basis of 17-ketosteroid excretions the possibility has already been considered that the adrenal cortex activity of R. S. and P. S. did not keep pace with their biologic ages. If so, this might account for the delayed appearance of axillary hair and would lend support to the above thesis. However, the fact that the growth of pubic hair in both boys rapidly attained adult characteristics and coincided with the rapid growth of the testes, while axillary hair remained absent and the 17-ketosteroid excretion remained relatively low, casts some doubt on the idea that the development of pubic hair is invariably conditioned by adrenal cortical activity. In these boys testicular androgen probably caused the development of the pubic hair. Also, some questions arise regarding the growth of axillary hair. In T. J. S., whose clinical picture of "dissociate virilism" was that of adrenal cortex hyperfunction and whose output of 17-ketosteroids was greatly increased, no axillary hair growth was present three years after the inception of the disorder. Even his pubic hair did not grow as rapidly as did that of R. S. and P. S. It appears that the factors which condition the growth of axillary and pubic hair, under normal and abnormal conditions, are complex and still not fully understood.

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19. Footnote 16. Nathanson, I. T.; Miller, R. B.; Towne, L. E., and Aub, J. C.: Close Correlation of Androgen and Creatinine Excretion in Normal Children, Endocrinology **28**:851-865 (June) 1941.

20. Albright, F. P.; Smith, P. H., and Fraser, R.: A Syndrome Characterized by Primary Ovarian Insufficiency and Decreased Stature: Report of 11 Cases with a Digression on Hormonal Control of Axillary and Pubic Hair, Am. J. M. Sc. **204**:625-648 (Nov.) 1942.

21. Kepler, E. J.; Peters, G. A., and Mason, H. L.: Addison's Disease Associated with Pubic and Axillary Alopecia and Normal Menses, J. Clin. Endocrinol. **3**:497-499 (Sept.) 1943.

Another interesting feature of the development of R. S. and P. S. was that their dental age was essentially normal for their chronologic age and not compatible with their accelerated gonadal, skeletal and somatic growth. This finding is in agreement with the more detailed and careful studies of Seckel and his associates.[22] These observations imply that the development of the teeth is governed by fundamental processes which probably reside outside of the endocrine system as we understand it. Unfortunately, an accurate record of the dental age of T. J. S. (adrenogenital syndrome) is not available.

Finally, the psychosexual behavior and mental characteristics of both R. S. and P. S. were entirely boyish; in fact, the mental development of R. S. was somewhat retarded. In spite of precocious genital growth neither child exhibited sexually aggressive trends, masturbatory tendencies or behavior characteristic of an adolescent. Thus, those portions of the central nervous system concerned with mental and emotional maturity seem to be peculiarly invulnerable to those influences which led to gonadal, somatic and skeletal advancement. Rather similar observations have been discussed by Gesell,[23] Seckel [22] and others.[24] That the central nervous system is not completely invulnerable in all circumstances is suggested by the studies of Keene and Stone,[24b] who found overt sexual behavior in six of 80 children with "precocious puberty." While T. J. S. (adrenogenital syndrome) did not exhibit overt sexual behavior, he did show certain abnormal behavior patterns, e. g., wearing his mother's nightgown, attraction to women's underwear and masturbatory acts. Similar peculiar behavior has been noted in some other boys suffering from adrenal cortex overactivity but it does not appear to be an invariable consequence.

SUMMARY

Clinical and laboratory data are presented on a family in which the father and two sons showed precocious genital and somatic growth. Another son has shown no abnormality. The term "contitutional" precocious development appears to be applicable to these cases. Another boy, who also was precociously developed but who suffered from adrenal cortex overactivity, was similarly studied.

Examination of the sequence of the appearance of maturity phenomena revealed that in these boys the general picture of growth in height and weight was like the adolescent "spurt" in growth of normal boys except for its occurrence at an abnormally early age. This suggests that the skeletal and probably the muscular systems respond in a fundamentally uniform manner whether stimulated to accelerated growth by normal or even by variously abnormal influences. Further, there seemed to be a relatively harmonious overgrowth of the skeletal and muscular systems. In the boys who suffered from the "constitutional" disorder, pubic hair growth rapidly assumed adult characteristics, as in normal boys, during the period

22. Seckel, H. P. G.; Scott, W. W., and Benditt, E. P.: Six Examples of Precocious Sexual Development: I. Studies in Diagnosis and Pathogenesis, Am. J. Dis. Child. **78**:484-515 (Oct.) 1949; II. Studies in Growth and Maturation, Am. J. Dis. Child. **79**:278-309 (Feb.) 1950.

23. Gesell, A.; Thoms, H.; Hartman, F. B., and Thompson, H.: Mental and Physical Growth in Pubertas Praecox: Report of 15 Years' Study of Case, Arch. Neurol. & Psychiat. **41**:755-772 (April) 1939.

24. (*a*) Dennis, W.: Effect of Pubertas Praecox on Age at Which Onset of Walking Occurs, Am. J. Dis. Child. **61**:951-957 (May) 1941. (*b*) Keene, C. M., and Stone, C. P.: Mental Status as Related to Puberty Praecox, Psychol. Bull. **34**:123, 1937.

of maximal increments in height and during maximal growth of the testes and penis. The bone age of these boys was concomitantly advanced. However, harmonious acceleration in the appearance of other phenomena of maturity, which would have been expected in normal boys of comparable biologic age, was not present. The following discrepancies were noted: the 17-ketosteroid excretion was considerably below that which would be expected for their "biologic" age, the appearance of axillary and facial hair was "delayed," dentition was not advanced, and they exhibited no pubescent personality or behavior. It is apparent that these boys did not pass through a normal "puberty."

The findings on these boys and on the boy with the adrenogenital syndrome suggest that in these circumstances their pubic hair and possibly their axillary hair growth was not necessarily conditioned by adrenal cortical activity. Also, it was not possible to correlate their 17-ketosteroid excretion with their degree of physical maturity. These observations are discussed. We have found, in general agreement with other investigators, that the teeth and the central nervous system apparently are peculiarly invulnerable to those influences which cause precocious development in other areas.

Dr. Grover Powers and Dr. Daniel C. Darrow of the Department of Pediatrics made these patients available to us for study.

POSSIBLE ROLE OF PLEUROPNEUMONIA-LIKE ORGANISMS IN ETIOLOGY OF DISEASE IN CHILDHOOD

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PLEUROPNEUMONIA-LIKE organisms, although known to produce disease in animals, are of questionable pathogenicity in human beings. They have been isolated repeatedly from the genitourinary tract, apparently as part of the normal flora of females, but possibly associated with nonspecific urethritis and Reiter's syndrome (nongonorrheal combination of arthritis, conjunctivitis and urethritis) in the male. The finding of similar pleuropneumonia-like organisms in blood cultures of two children with nonthrombocytopenic purpura and in one child with brain abscess and meningitis leads to the consideration of possible pathogenicity of such organisms in unsuspected situations in childhood.

Pleuropneumonia-like organisms are a group of extremely pleomorphic, filtrable, poorly staining bodies that can be grown on enriched artificial mediums. Cultures consist of small granules and fine filaments. The small granules enlarge to form soft, spherical masses of varied size which finally rupture and free numerous daughter granules. The method of reproduction is in contrast to the usual bacterial fission. The colonies are often but 10 to 20 microns in diameter and can be seen only by microscope. In growth they not only increase on the surface but extend into the solid medium. Granules presenting the appearance of these organisms can be found in cultures of various bacteria and may represent variants or symbionts of that species of bacteria; others possibly represent a class in themselves. Pleuropneumonia-like organisms have also been found in soil and sewage, where they are presumably saprophytes. However, in cattle and rodents they have been identified as etiological agents of diseases which are characterized by chronicity and, in some instances, by a migratory polyarthritis. No matter what the source, the pleuropneumonia strains appear to be morphologically and culturally similar. However, antigenically they appear to vary.

REVIEW OF LITERATURE

Nocard and Roux [1] in 1898 from a plague among cattle first cultured bovine pleuropneumonia organisms, but microscopic observation was made first in 1910 by

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1. Nocard and Roux: Le microbe de la péripneumonie, Ann. Inst. Pasteur **12**:240, 1898.

Bordet.[2] A similar type of organism was isolated in 1925 by Bridré [3] from sheep with contagious agalactia. A decade later Klieneberger [4] published her findings on pleuropneumonia-like organisms associated with Streptobacillus moniliformis. This study stimulated further investigation by both British and American workers on the significance of this group of organisms in disease in man and in animals.

Klieneberger, in describing the pleuropneuomnia-like organisms, designated them as L phases. The L_1 phase [5] was thought to be a symbiont of S. moniliformis. However, Dienes,[6] Heilman,[7] Smith [8] and Brown and Nunemaker [9] were of the opinion that it represented a variant rather than a symbiont. The L_2 organism was isolated from guinea pigs and associated with the Streptococcus.[4] The L_3 phase was isolated from bronchiectatic lung lesions which are so common in old rats.[10] The L_4 phase was isolated from rats with spontaneous polyarthritis.[11] Interestingly, gold salts appeared to be of prophylactic value against experimental production of this disease. The L_5 phase was isolated from mice and was observed to produce an exotoxin which had a striking affinity for the cerebellum and produced the entity known as "rolling disease." [12] The L_6 phase of Klieneberger was isolated from brains of mice previously inoculated with blood of splenectomized mice infected with Eperythrozoon coccoides.[11d] Another phase of pleuropneumonia organism which is designated as M 55 was reported by Klieneberger [13] from a type of mouse arthritis. As this phase has not yet been classified antigenically, it has not been

2. Bordet, J.: La morphologie du microbe de la péripneumonie des bovidés, Ann. Inst. Pasteur **24**:161, 1910.

3. Bridré, J., and Donatien, A.: Le microbe de l'agalaxie contagieuse du mouton et de la chevre, Ann. Inst. Pasteur **39**:925, 1925.

4. Klieneberger, E.: Natural Occurrence of Pleuropneumonia-Like Organisms in Apparent Symbiosis with Streptobacillus Moniliformis and Other Bacteria, J. Path. & Bact. **40**:93, 1935.

5. Klieneberger.[4] Klieneberger, E.: Some New Observations Bearing on the Nature of the Pleuropneumonia-Like Organisms Known as L_1 Associated with Streptobacillus Moniliformis, J. Hyg. **42**:485, 1942.

6. Dienes, L.: L Organisms of Klieneberger and Streptobacillus Moniliformis, J. Infect. Dis. **65**:24, 1939.

7. Heilman, F. R.: A Study of Asterococcus Muris (Streptobacillus Moniliformis): Morphologic Aspects and Nomenclature, J. Infect. Dis. **69**:32, 1941.

8. Smith, W.: Cervical Abscesses of Guinea Pigs, J. Path. & Bact. **53**:29, 1941.

9. Brown, T. M., and Nunemaker, T. C.: Rat-Bite Fever: Review of American Cases with Reevaluation of Etiology; Report of Cases, Bull. Johns Hopkins Hosp. **70**:201, 1942.

10. Klieneberger, E., and Steabben, D. B.: On a Pleuropneumonia-Like Organism in Lung Lesions of Rats, with Notes on the Clinical and Pathological Features of the Underlying Condition, J. Hyg. **37**:143, 1937; On the Association of the Pleuropneumonia-Like Organisms L_3 with Bronchiectatic Lesions in Rats, ibid. **40**:223, 1940.

11. (*a*) Woglom, W. H., and Warren, J.: Pyogenic Virus in Rat, Science **87**:370, 1938. (*b*) Klieneberger, E.: Pleuropneumonia-Like Organisms of Diverse Provenance: Some Results of an Enquiry into Methods of Differentiation, J. Hyg. **38**:458, 1938; (*c*) Studies on Pleuropneumonia-Like Organisms: The L_4 Organism as the Cause of Woglom's "Pyogenic Virus," ibid. **39**:260, 1939. (*d*) Findlay, G. M.; MacKenzie, R. D.; MacCallum, F. O., and Klieneberger, E.: The Etiology of Polyarthritis in the Rat, Lancet **1**:7, 1939.

12. Findlay, G. M.; MacKenzie, R. D.; MacCallum, F. O., and Klieneberger, E.: Rolling Disease, Lancet **2**:1511, 1938. Sabin, A. B.: Identification of the Filtrable, Transmissible, Neurolytic Agent Isolated from Toxoplasma-Infected Tissue as a New Pleuropneumonia-like Microbe, Science **88**:575, 1938. Sullivan, E. R., and Dienes, L.: Pneumonia in White Mice Produced by a Pleuropneumonia-like Microorganism, Proc. Soc. Exper. Biol. & Med. **41**:620, 1939.

13. Klieneberger, E.: The Pleuropneumonia-Like Organisms: Further Studies and a Descriptive Account of Recently Discovered Types, J. Hyg. **40**:204, 1940.

assigned a place in the L series. Sabin and Johnson [14] reported B, C, D and E strains which they isolated from conjunctiva, respiratory tract and brain of mice. These strains when given intravenously to mice produced arthritis. Laidlaw and Elford [15] isolated three saprophytic pleuropneumonia-like strains from sewage and Seiffert [16] a strain from soil. The L strains have been differentiated and classified according to their antigenic and serologic reactions.

Tang, Wei and Edgar [17] and Turner [18] observed the biochemical reactions of the bovine pleuropneumonia organisms. These investigators also attempted to demonstrate that the organisms have definite life cycles. Dienes and Edsall [19] studied the L_1 phase of Klieneberger and observed that the pathogenicity of the L_1 phase varied with the strain and that the organism was not a degenerative form of bacteria but a definite and viable form of organism. Dienes,[20] as well as Brown and Nunemaker,[9] further demonstrated the reversion of L_1 phase to the S. moniliformis. Pierce [21] reported that penicillin in a culture of S. moniliformis enhanced the appearance of L_1 phase. Higher concentrations were observed to inhibit all growth. Dienes and his co-workers [22] have demonstrated that with gram-negative bacilli and gonococci addition of penicillin to the medium caused production of spherical bodies which were hard to differentiate from pleuropneumonia-like organisms. In the case of Escherichia coli and Hemophilus influenzae the organisms had all the characteristics of the pleuropneumonia group. Brown and Hayes [23] found L type colonies in pure cultures of Neisseria gonorrhoeae. They were also able to separate out the L type organisms but were unable to have them revert.

Dienes and Edsall [19] in 1937 first reported finding the organisms in an abscess of a Bartholin gland. Subsequently numerous workers [24] have reported finding the

14. Sabin, A. B., and Johnson, B.: Search for Microorganisms of the Pleuropneumonia Group in Rheumatic and Non-Rheumatic Children, Proc. Soc. Exper. Biol. & Med. **44**:565, 1940.

15. Laidlaw, P. P., and Elford, W. J.: New Group of Filtrable Organisms, Proc. Roy. Soc., London, s.B **120**:292, 1936.

16. Seiffert, G.: Ueber das Vorkommen filtrabler Mikroorganismen in der Natur und ihre Züchtbarkeit, Zentralbl. f. Bakt. (Abt. 1) **139**:337, 1937.

17. Tang, F. F.; Wei, H., and Edgar, J.: Further Investigations on Causal Agent of Bovine Pleuropneumonia, J. Path. & Bact. **42**:45, 1936.

18. Turner, A. W.: A Study of the Morphology and Life Cycles of the Organism of Pleuropneumonia Contagiosa Bovum (Borrelomyces Peripneumoniae Nov. Gen.) by Observation in the Living State Under Dark-Ground Illumination, J. Path. & Bact. **41**:1, 1935.

19. Dienes, L., and Edsall, G.: Observations on the L-Organism of Klieneberger, Proc. Soc. Exper. Biol. & Med. **36**:740, 1937.

20. Dienes, L.: Further Observations on the L-Organism of Klieneberger, Proc. Soc. Exper. Biol. & Med. **39**:365, 1938.

21. Pierce, C. H.: Streptobacillus Moniliformis: Its Associated L_1 Form and Other Pleuropneumonia-Like Organisms, J. Bact. **43**:780, 1942.

22. Dienes, L.; Ropes, M. W.; Smith, W. E.; Madoff, S., and Bauer, W.: Medical Progress: The Role of Pleuropneumonia-Like Organisms in Genitourinary and Joint Diseases, New England J. Med. **238**:509, 1948.

23. Brown, T. M., and Hayes, G. S.: Isolation of Microorganisms of the Pleuropneumonia Group from Apparently Pure Cultures of the Gonococcus (Neisseria Gonorrhoeae), J. Bact. **43**:82, 1942.

24. (*a*) Klieneberger, E., and Nobel, E.: Pleuropneumonia-like Organisms in Human Vagina, Lancet **2**:46, 1945. (*b*) Salaman, M. H., and others: Isolation of Organisms of Pleuropneumonia Group from Genital Tract of Men and Women, J. Path. & Bact. **58**:31, 1946. (*c*) Beveridge, W. I. B.; Campbell, A. D., and Lind, P. E.: Pleuropneumonia-like Organisms in Cases of Non-Gonococcal Urethritis in Man and in Normal Female Genitalia, M. J. Australia **1**:179, 1946.

organism in cervical cultures from normal women, as well as from those with pelvic infections. In males they have been reported in the discharge in nonspecific urethritis.[25] Dienes and co-workers [22] in a review of the subject felt that although pleuropneumonia-like organisms may be part of the normal bacterial flora of the female genital tract evidence of pathogenicity was more apparent in the male, in that every person whose culture proved positive had urethritis, prostatitis or cystitis. Interestingly, of the 58 males with positive cultures 18 had acute arthritis, and nine of these had findings compatible with Reiter's syndrome. In two of this last group organisms were isolated from synovial fluid. These investigators also examined secretions from respiratory tract and conjunctiva, pleural and spinal fluids and stools and observed that in the absence of penicillin all cultures were negative for the organism. It was emphasized that in the presence of penicillin in either patient or culture medium cultures from the respiratory tract may be positive for pleuropneumonia-like organisms, variants possibly of H. influenzae, while variants of the gonococcus may similarly appear in cultures of discharge from patients with gonococcic urethritis. The pleuropneumonia-like strain isolated from patients with Reiter's syndrome was sensitive to streptomycin. Brown and his associates [26] further showed that oral administration of aureomycin produced a uniform disappearance of demonstrable pleuropneumonia-like organisms from the genitourinary tract of persons with and without joint disease. In many with a picture of rheumatoid arthritis there occurred improvement of the joint manifestations. Herschberger, Dantes and Schwartzman [27] reported the isolation of an organism belonging to either a pleuropneumonia-like or a Grahamella group from the blood of a patient with subacute bacterial endocarditis. Present evidence seems to indicate that the organism described belongs to the Grahamella group. Brown and Nunemaker [9] implied that the L_1 phase may be pathogenic for human beings but failed to obtain it directly from patients with rat bite fever, isolating it only from cultures of S. moniliformis from patients with the disease.

Little is known about the properties of the human strains. Serologically there is evidence to show differences among human strains and between human and animal strains. The human strains in the experience of Dienes,[22] except in one instance with one litter of young mice, have not proved pathogenic for mice, rats or guinea pigs. Identification in microscopic preparations of lesions is practically impossible, as organisms are not visible with the usual stains. Culture at present seems to afford the only method for their recognition.

Dienes,[28] in a comprehensive report concerning morphologic aspects and the nature of the pleuropneumonia-like organism, stated that the organisms isolated from rats, mice and man often appear as small bacilli with bipolar staining and that the group presents no properties not shared by bacteria. He felt that the small

25. Beveridge and others.[24c] Beveridge, W. I. B.: Isolation of Pleuropneumonia-like Organisms from Male Urethra, M. J. Australia **2**:479, 1943.

26. Brown, T. M.; Wichelhauser, R. H.; Robinson, L. B., and Merchant, W. R.: The in Vivo Action of Aureomycin on Pleuropneumonia-like Organisms with Various Rheumatic Diseases, J. Lab. & Clin. Med. **34**:1404, 1949.

27. Herschberger, C.; Dantes, D. A., and Schwartzman, G.: Case of Subacute Bacterial Endocarditis Caused by Unusual Microorganism Related to "Pleuropneumonia-like" or Grahamella Group, J. Mt. Sinai Hosp. **12**:295, 1945.

28. Dienes, L.: Morphology and Nature of the Pleuropneumonia Group of Organisms, J. Bact. **50**:441, 1945.

gram-negative bacilli, such as Pasteurella and Hemophilus, often show definite similarity to the group in reproduction, softness, fragility and poor staining. Thus, he placed the organism near the genera of Pasteurella and Hemophilus and implied that they may be intermediates between small bacteria and large viruses such as that of lymphogranuloma venereum. Electron microscopy [29] shows pleuropneumonia-like organisms to be highly pleomorphic bacilli with a well defined cell wall and cytoplasm.

METHODS

In the cases to be reported blood cultures were made on Difco Kracke blood culture medium and brain-heart infusion broth. Growth occurred only in the latter medium and became apparent after three to four days of incubation at 37 C. as a slight cloudiness of the supernatant broth and a fine granular sediment. Smears of the cloudy broth or sediment stained by Gram's technic or methylene blue revealed no organisms. Subcultures from the broth onto blood agar showed no growth. In order to obtain growth on subculture, special enriched mediums had to be used. Among such mediums were veal infusion broth, tryptose broth or tryptose agar enriched by the addition of dextrose, peptone and ascitic fluid, horse serum or blood. On solid mediums minute colonies which grew on the surface and extended into the agar appeared in four days. Colonies were further subcultured by the method described by Dienes.[6] Small sections of agar containing the colonies were removed and placed either in enriched broth or on the surface of enriched tryptose agar plates. In the latter method the section was removed from the surface in 48 hours, and growth was observed on the plate after further incubation. The organisms were stained by a technic devised by Dienes.[6] One drop of saturated alcoholic solution of methylene blue was placed on a cover slip and allowed to evaporate. One drop of liquid culture medium or a thin block of agar was placed on a clean glass slide and covered with the cover slip which contained the dye. Several minutes were allowed to elapse for complete penetration of the stain before observation microscopically. Preparations were sealed with paraffin to minimize evaporation.

REPORT OF CASES

Our first patient, J. R., who had purpura and from whose blood we isolated a pleuropneumonia-like organism, was a 3 year old white boy who was admitted to the Babies and Children's Hospital of Cleveland with an indolent ulcer on the index finger of the left hand of seven days' duration, numerous discrete erythematous, as well as petechial, lesions varying from 5 to 10 mm. in diameter on both lower extremities and buttocks of two days' duration (fig. 1) and swelling of the dorsum of the right hand and right knee of one day's duration. There was no adenopathy or splenomegaly. The history further disclosed that the child lived on a farm and often played in a chicken house, where he might have come in contact with the excreta of field mice. Laboratory studies revealed a white blood cell count of 13,400, of which 90 per cent were polymorphonuclear leukocytes, 7 per cent lymphocytes and 3 per cent monocytes. The red blood cell count, thrombocyte (platelet) count, bleeding and clotting times and sedimentation rate were all within normal limits. Because the possibility of rat bite fever due to S. moniliformis was considered, blood cultures in enriched mediums were obtained before therapy was started. During the four days following admission, despite penicillin therapy, there was an increase in the child's symptoms. A soft tissue swelling measuring 10 cm. in diameter occurred on the left side of his head. Episodes of abdominal pain developed which were followed by semiliquid stools consisting largely of blood, and there was an increase in the petechial lesions on the buttocks. During this period the child's temperature rose daily to approximately 38 C. (100.4 F.). Subsequently over the next seven days the child made a gradual but complete recovery. During his hospitalization three blood cultures, one before and two after penicillin was administered, proved positive for pleuropneumonia-like organisms.

Growth in blood cultures taken on admission was not evident until the fourth day of incubation. At that time a fine granular sediment clinging to the side of the flask was observed in the

29. Weiss, L. J.: Electron Micrographs of Pleuropneumonia-like Organisms, J. Bact. **47**:523, 1944. Smith, W. E.; Hillier, J., and Mudd, S.: Electron Micrograph Studies of 2 Strains of Pleuropneumonia-like (L) Organisms of Human Derivation, ibid. **56**:589, 1948.

brain-heart infusion broth. Stained specimens of these cultures by ordinary technics, Gram's carbolfuchsin and Wright's methods, failed to reveal any visible organisms. Similar samples stained in wet mount with alcoholic methylene blue revealed the presence of pleomorphic bodies closely resembling pleuropneumonia-like organisms. Many small coccic forms 0.5 to 0.7 micron in diameter and a few small curved bacillary forms varying in length from 1 to 2 microns were observed. Large globoid bodies, approximately 8 to 10 microns in diameter, containing heavy chromatin-staining granules were occasionally seen. No weblike tentacles were observed.

Blood cultures made by the pour plate technic at the patient's bedside, using tryptose agar containing an added 1 per cent peptone and 1 per cent dextrose and also heart infusion agar, revealed the presence of minute colonies after four days' incubation. Wet mount preparations made of thin agar sections containing these colonies showed them to vary in size from 150 to 400 microns. The central portion of the colony appeared to be dense, while on the periphery there were many small, scattered, globoid bodies which appeared to be distinct and separated from one another. Subculture of these colonies to veal infusion, enriched tryptose and

Fig. 1.—Photographs of J. R., showing discrete erythematous and petechial lesions. Note a central dark area in many of the individual lesions suggesting an embolic phenomenon.

thioglycollate broths was again found positive for similar micro-organisms. After numerous subcultures over a one month period, there was no change in the character of the organisms and no apparent reversion to a bacillary form resembling the S. moniliformis.

Broth from positive cultures and 1 ml. of the patient's blood were inoculated intraperitoneally into each of six 3 to 4 week old white Swiss mice with negative results. A similar group of mice, after receiving one drop intranasally of the broth from positive cultures, showed consolidation of the lungs when killed on the seventh day. Cultures in broth made from these lung suspensions revealed the presence of an alpha hemolytic Streptococcus and a pleuropneumonia-like organism. Transfer of the lung suspensions to other mice by the intranasal route again produced similar lung lesions and positive cultures for pleuropneumonia-like organisms. In our control group no pleuropneumonia-like organisms were observed.

Our second patient, G. O., an 8 year old white boy, was admitted with a history of intermittent migratory arthritis and petechial rash involving chiefly the extremities of five weeks' duration. During this period he also had several episodes of abdominal pain associated with the appearance of bright red blood in the stools and one episode of localized edema over the lumbar part of the

spine and over the posterior portion of the left calf. In the history it was further noted that he had received a human bite one week before the onset of his symptoms. Physical examination on admission revealed a well developed but poorly nourished white boy who was complaining of generalized muscle tenderness. Over the skin of extremities, buttocks and genitalia there were numerous petechiae (fig. 2). There was no adenopathy of note. The abdomen was slightly distended and tympanitic. The liver was felt 2 fingerbreadths below the costal margin. The spleen and kidneys were not palpable. Laboratory data except for evidence of a mild anemia were essentially within normal limits.

The child remained in the hospital for seven weeks. During this period he had an occasional temperature elevation to 38.4 C. (101.1 F.). Exacerbation and remission of abdominal pain and

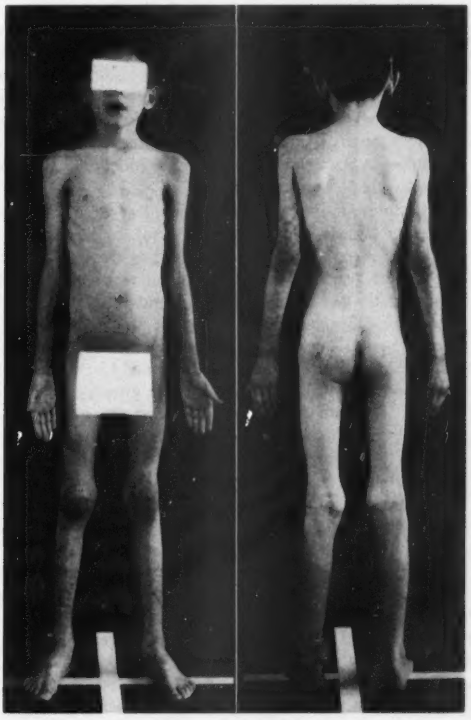

Fig. 2.—Photographs of G. O., showing the distribution of the petechial eruption.

petechiae continued without any obvious relationship between the two. Repeat urinalyses showed the presence of albumin and blood microscopically. He was tried successively on courses of treatment with penicillin, tripelennamine (pyribenzamine®) hydrochloride, diphenhydramine (benadryl®) hydrochloride, streptomycin and paraaminobenzoic acid without any noticeable effect on the course of his disease or his blood cultures. Two weeks after the patient's discharge, severe abdominal pain developed with blood in the stools, and he was readmitted. The abdomen at this time was conspicuously distended and diffusely tender. No masses were palpable. Because of the extreme distention roentgenograms, with a barium sulfate enema, were taken, and a diagnosis of intussusception was made. This was confirmed on surgical intervention in which it was necessary to resect 15 inches (38 cm.) of the terminal portion of the ileum. The pathological report on the operative specimen showed an organizing acute inflammation of submucosal and subserosal layers of the ileum, telangiectases of the ileum and acute and chronic

inflammation of the mesenteric lymph nodes. The postoperative course was essentially uneventful. Although he continued to have episodes of abdominal pain and new crops of petechiae, they became less prominent; his albuminuria and hematuria cleared, and he was finally discharged on his thirtieth hospital day. He was subsequently seen at three month intervals over a one year period. The severity and frequency of his abdominal pain, petechial eruptions and soft tissue and joint swellings gradually abated. On his last visit the results of physical examination and laboratory studies were all normal. Blood cultures taken during his first and second hospital admissions and on the first three follow-up visits were positive for pleuropneumonia-like organisms.

Nine blood cultures made over a period of six weeks during his first hospital admission revealed small coccic filamentous micro-organisms morphologically similar to those of the pleuropneumonia-like group. Cultures of cerebrospinal fluid were negative.

Tests were made with this specific strain of pleuropneumonia-like organism to determine the sensitivity to streptomycin (100 micrograms), penicillin (100 units), sulfadiazine (25 mg.), methylrosaniline chloride (10 micrograms), methylene blue (10 micrograms), brilliant green (10 micrograms), acid fuchsin (10 micrograms) and trinitrophenol (10 micrograms). Samples removed at one and 24 hours from culture tubes containing broth and the above agents previously inoculated with 0.05 ml. of a four day culture were found to produce luxuriant growth. The organisms survived and grew in the original culture tube containing the agents. None of the dyes or drugs tested inhibited this organism.

Growth of this organism in the presence of the dyes used appeared tto cause distinct changes morphologically from coccic to occasionally filamentous forms. In the presence of methylrosaniline chloride many small minute granules with filaments extending from these bodies were produced. The growth in carbolfuchsin produced only round yeastlike forms which appeared to stain lighter in the central portion, giving the appearance of being concave. Growth in trinitrophenol was sparse. The filamentous form only was observed, and it stained poorly. In the presence of methylene blue the predominant shape was large yeastlike forms containing many granular cell-like bodies peripherally and centrally located. These cell-like bodies were deeply stained. Growth in brilliant green produced bodies similar to those growing in the presence of methylrosaniline chloride. The only difference observed was that the small granules and filaments stained poorly. The filtrability of this strain of pleuropneumonia-like organism was determined by pooling several broth cultures and passing them through a sterile Berkefeld N filter. The clear filtrate was transferred to 10 tubes of tryptose broth and incubated. Luxuriant growth of pleuropneumonia-like organisms similar in morphologic appearance to the original isolation was observed in all tubes. Many attempts to transfer this specific strain to enriched solid mediums or to animals met with failure.

Our third patient, D. E., in whom we isolated a pleuropneumonia-like organism presented an entirely different clinical picture. He was a 5½ year old white boy with congenital heart disease and cyanosis who was admitted to the hospital because of daily elevation in temperature over a two week period. Abnormal physical findings were limited to the heart, clubbing of the fingers and cyanosis. Laboratory studies revealed a red blood cell count of 8,500,000, with 120 per cent hemoglobin and a white blood cell count of 12,900, of which 78 per cent were polymorphonuclear leukocytes, 18 per cent lymphocytes and 4 per cent monocytes. Urinalysis showed no abnormality. Because subacute bacterial endocarditis was suspected, blood cultures were taken over a two week period before onset of any chemotherapy. At first all the blood cultures were considered negative. Fourteen days after admission, as he was still showing a daily rise in temperature to 38.5 C. (101.3 F.), administration of sulfadiazine and penicillin was started. Seven days later, while he was still receiving chemotherapy, semistupor and meningeal signs developed. A lumbar puncture revealed grossly purulent spinal fluid containing 47,700 cells, of which 99 per cent were polymorphonuclear leukocytes; protein measured 400 mg. per 100 ml.; sugar was absent. Clinically we then felt that the child had had a brain abscess which had ruptured into the ventricular system producing a meningitis. Microscopic examination of the spinal fluid revealed spherical bodies which were poorly stained. Our first impression was that they represented yeast cells. However, on culture they appeared to be pleuropneumonia-like organisms. At that time when we reviewed the blood cultures, did special subcultures and employed the stains outlined previously, we realized that they too had been positive for pleuropneumonia-like organisms. Treatment with potassium iodide was tried when we thought

the patient had a yeast infection. Later he again received penicillin and streptomycin without alteration in his course. At necropsy a cerebral abscess in the left frontal lobe and fibrinopurulent cerebrospinal meningitis were observed. The heart did not show evidence of an endocarditis. Cultures of the ventricular fluid at necropsy also revealed a pleuropneumonia-like organism.

Blood cultures from this patient in heart infusion broth were observed to become cloudy on the fourth day of incubation. On examination of the flask with the use of a hand lens, the growth appeared as a finely granular sediment which tended to cling to the sides of the glass culture flask. Alcoholic methylene blue stains revealed the presence of small round bodies containing scattered dark-staining granules. Many of the bodies appeared to have ruptured, releasing a network of filaments. Morphologically they appeared similar to pleuropneumonia-like organisms. These structures were observed in all blood and cerebrospinal fluid cultures. In direct examination of the cerebrospinal fluid faintly staining round bodies, definite in shape but varying from 1 to 4 microns in diameter, were seen. Growth in veal infusion broth containing 0.1 per cent agar formed a cloudy granular appearance at the surface. On solid mediums the colonies were small, and, when observed with a hand lens, minute central dark areas could be seen. The macroscopic colonies as just described, observed under the low power objective of the microscope, were found to be made up of many minute colonies containing what appeared to be cholesterol-like bodies. Subcultures in broth of small blocks of agar containing the colonies were observed to form small round bodies with filaments in weblike clusters as previously described.

One milliliter of the broth from positive cultures inoculated intraperitoneally into young and adult mice failed to produce any effect. One drop of broth culture previously inoculated with cerebrospinal fluid and containing luxuriant growth of the pleuropneumonia-like organisms was instilled intranasally into four partially anesthetized 4 week old Swiss mice. On the fourth day after inoculation one of the mice was found dead. The remaining three were killed, and their lungs were removed aseptically. All lungs were observed to have large areas of consolidation. Culture of the lung suspension again revealed pleuropneumonia-like organisms. On transfer of the lung suspension by the intranasal route to a second group of mice, identical results were obtained.

COMMENT

The presence of pleuropneumonia-like organisms in cultures can easly be missed in routine laboratory examinations. Although brain-heart infusion broth apparently contains sufficient nutrient for the organism's growth in three to four days and is used routinely by us for blood cultures, we still failed initially in one case, that of patient D. E., to recognize the organism. Failure probably resulted from lack of proper staining technics and from attempts to subculture on blood agar, a medium not supporting growth of this organism. The organism was isolated when the proper technics in staining and subculturing were used. Photomicrographs are presented (figs. 3 to 9).

The organisms have not been classified serologically; hence their relationship to other strains isolated from animals or human beings is not known.

Because the clinical findings in our first case suggested rat bite fever, the organisms were thought possibly to be the L_1 phase. However, Brown and Nunemaker [9] in a study of proved cases failed to grow the L_1 phase without first obtaining the S. moniliformis. Also they were able to cause L_1 phase to revert to the Streptobacillus, something we were unable to do. The absence of fever, the presence of abdominal pain and blood in the stools, plus migratory arthritis and purpura in both patients, and the failure of the disease in patient G. O. to respond to penicillin and streptomycin suggested the clinical diagnosis of Henoch-Schönlein purpura rather than rat bite fever. Both cases possibly differ from the usual case of Henoch-Schönlein purpura in that the first patient, J. R., had a splinter in his finger followed by an indolent ulcer and the second, G. O., had sustained a human bite before the

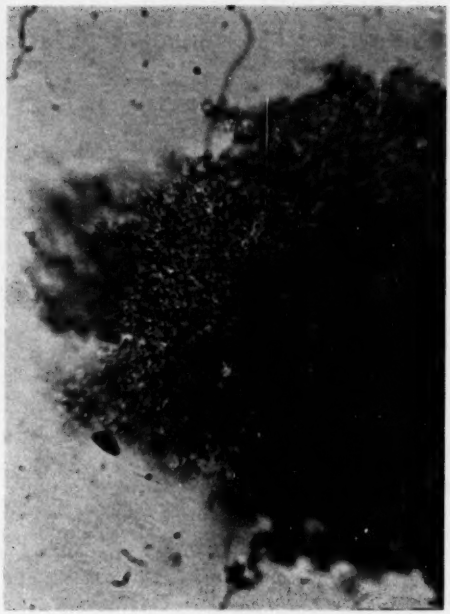

Fig. 3.—Photomicrograph of methylene blue-stained preparation made from broth culture of organisms isolated from patient J. R. The organisms appear as rods and small, heavily stained globoid bodies. × 900.

Fig. 4.—Photomicrograph of unstained colony of pleuropneumonia-like organisms isolated from patient G. O. and grown on enriched blood agar. Many small bodies or small colonies, loosely connected, appear to make up the larger colony. × 100.

Fig. 5.—Photomicrograph of methylene blue–stained wet mount preparation made from broth culture of organisms isolated from patient G. O. Note the globoid and ring forms within which are seen smaller granules. × 900.

Fig. 6.—Photomicrograph of methylene blue–stained wet mount preparation made from broth culture of organisms isolated from patient G. O. Small round globoid forms are seen in contrast with erythrocytes (darkly stained spherical forms). × 900.

Fig. 7.—Photomicrograph of wet mount preparation stained with methylene blue from broth culture of organisms isolated from patient D. E. Note the large globoid bodies containing smaller heavily stained granules. × 2,110.

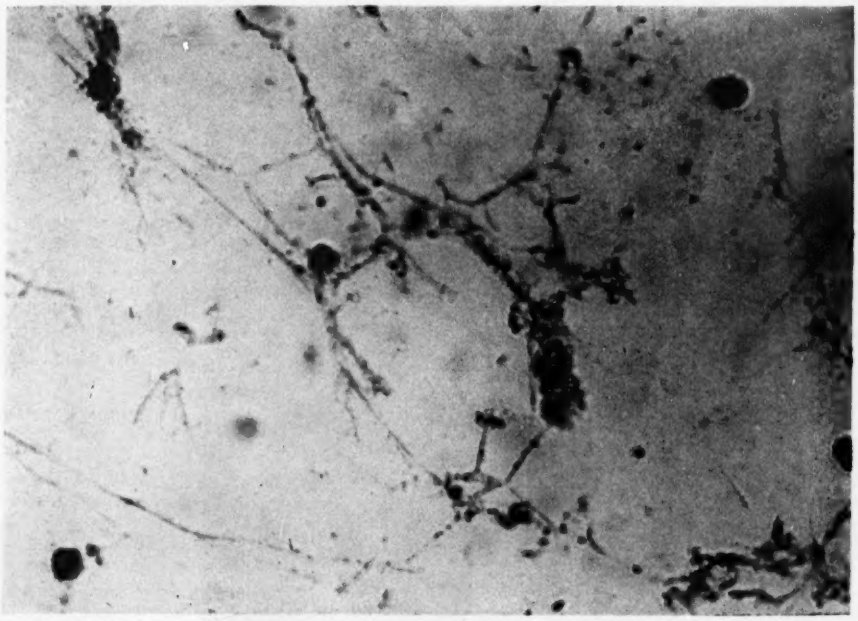

Fig. 8.—Photomicrograph of wet mount preparation stained with methylene blue from broth culture of organisms isolated from patient D. E. Note large irregular globoid bodies containing small darkly stained granules. The globoid bodies appear to be connected by a series of weblike tentacles. × 1,785.

onset of the purpura. That the finding of pleuropneumonia-like organisms was not a coincidence seems indicated by our finding the organism in blood culture on three occasions in the case of J. R. and on 13 occasions over an 18 month period in the case of G. O. The initial blood cultures in both patients were taken before onset of treatment with penicillin or other chemotherapeutic agents. Interestingly, the disease in these two patients presented chronicity and polyarthritis, characteristics seen so often in animal infections with pleuropneumonia-like organisms and in human beings from whom this organism has been isolated. That all cases presenting the picture of Henoch-Schönlein purpura are not related to the presence of a pleuropneumonia-like organism is suggested by our failure to isolate the organism

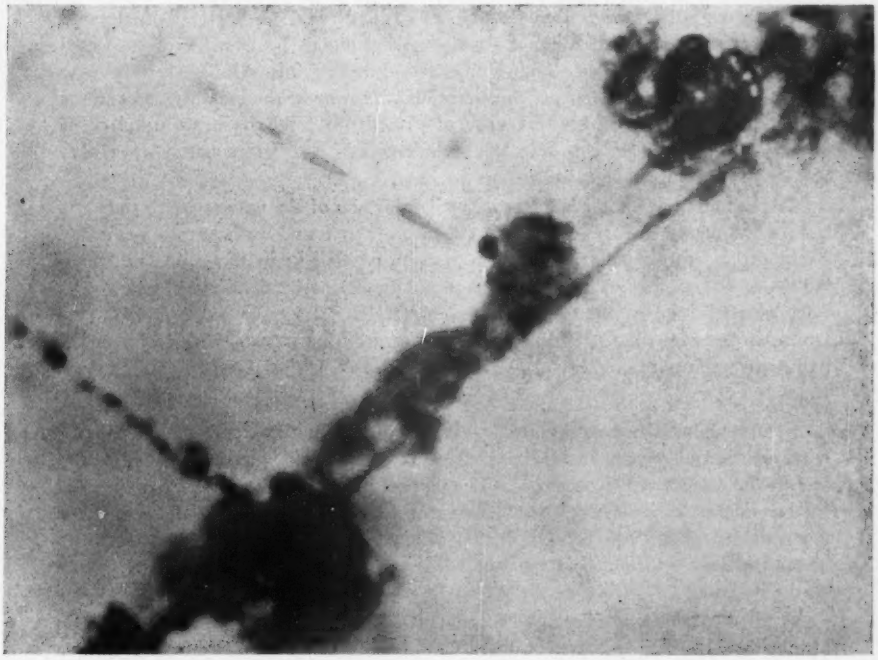

Fig. 9.—Photomicrograph of wet mount preparation stained with methylene blue from broth culture of organisms isolated from patient D. E. × 5,077.

in other patients with this syndrome. However, in a third patient with nonthrombocytopenic purpura, migratory arthritis, abdominal pain and blood in the stools, an initial blood culture was positive for pleuropneuomnia-like organisms. A description was not included in our case reports because all subsequent cultures proved to be negative.

In our third patient, D. E., we isolated the organism from the blood on seven occasions, four before onset of chemotherapy, from the spinal fluid on three occasions and from the ventricular fluid at necropsy.

As a check of our findings in the blood cultures of these patients, a study was undertaken to determine whether similar organisms might be present in otherwise

negative blood cultures. During a two month period approximately 200 routine blood cultures were examined for the presence of a granular sediment. On the fourth and fifth days of incubation 50 of these cultures proved suggestive. In these, by smear and methylene blue wet mount, numerous oval bodies singly and in clumps with a stipple staining of the cytoplasm, resembling pleuropneumonia-like organisms, were seen. Certain of these bodies measured approximately 2 microns in diameter, while others measured 7 to 10 microns and contained larger deep-staining granules. Occasionally filaments were observed. These blood cultures were subcultured, using 0.1 ml. of broth in 5 ml. of three types of highly enriched liquid mediums. Thirty-five of the 50 cultures were again suggestive. However, on a third subculture, all proved negative. If the initial suggestive blood culture were passed through Berkefeld N filters, all subcultures were negative. Attempts to produce growth on solid mediums or disease in animals by transfer of suspected positive broth culture failed. The significance of finding this sediment in otherwise negative blood cultures is as yet undetermined. However, the inability to continue to obtain positive subcultures, absence of growth on solid mediums and lack of filtrability appear to indicate that this sediment is of a different nature from that obtained from culture of blood in our patients.

The sensitivity of the organism isolated from one of the patients with purpura, G. O., was tested in vitro, and the organism was found resistant to penicillin, streptomycin and sulfadiazine. In this patient, as well as in the child with meningitis, there was also no clinical response to sulfadiazine, penicillin or streptomycin. Lack of sensitivity of these organisms suggests that they are different from the strains isolated by Dienes [22] from the human genitourinary tract, which were sensitive to streptomycin.

SUMMARY

Pleuropneumonia-like organisms were isolated from the blood of two patients with the clinical picture of Henoch-Schönlein purpura, in one on three occasions and in the second on 13 occasions. The clinical picture in the second patient is of further interest in indicating the extreme care that is necessary in evaluation of the complaint of abdominal pain in these patients. This child after many bouts of abdominal pain with blood in the stools had an intussusception requiring resection of the ileum.

A third patient is presented with congenital heart disease of cyanotic type, brain abscess and meningitis, from whose blood, spinal fluid and ventricular fluid a pleuropneumonia-like organism was isolated.

The organisms were not classified serologically so that their relationship to other isolated strains or to one another is not known.

RELATIONSHIPS BETWEEN BLOOD LIPID AND BLOOD PROTEIN LEVELS IN THE NEPHROTIC SYNDROME

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THE BLOOD chemistry of the nephrotic syndrome is characterized by (1) lipemia, with elevation of all the plasma lipids, and (2) hypoproteinemia, with low albumin and gamma globulin fractions.

The cause of the lipemia is obscure. The low protein level is probably not (as the coincidence of lipemia with hypoproteinemia and edema might suggest) the sole determining factor, for in malnutrition when the proteins are also low the lipids show no consistent elevation. In the dog they may be unaffected [1] or rise moderately [2]; in man they tend to be decreased rather than elevated.[3]

However, it is believed that the lipemia is related in some way to the abnormal plasma protein levels in nephrosis. This view receives support from demonstrations that in nephrotic blood the quantity of lipid chemically associated with specific plasma protein fractions (for example, beta globulin) may be increased above normal.[4]

To investigate this relation further, we determined the levels of the lipids and proteins of the blood in nephrotic children at intervals during the course of the disease and analyzed these data for evidence of correlation between the lipid levels and protein levels. The results of this analysis are presented in the following report.

PROCEDURE

Postabsorptive total and fractional blood protein and lipid levels of eight nephrotic children aged from 2 to 10 years were obtained at intervals over a three to six month period. These

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TABLE 1.—*Total and Fractional Lipid and Protein Val*

Patient	Age, Yr.	Date	Blood Fats, Mg./100 Cc.							Increase in Blood Fats, % Total			Serum Proteins, Gm./100 Cc.		
			Total Lipid	Phospho-lipid	Total Cholesterol	Ester Cholesterol	Free Cholesterol	Cholesterol Ester	Neutral Fat	Ester Choles-terol: Total Cholesterol	Due to Total Cholesterol	Due to Neu-tral Fat	Due to Phos-pholipid	Total Protein	Total Albumin	Total Globulin
A. A.	2½	2/11/48	1,775	375	323	193	130	334	936	0.60	10	72	15	...	...	...
		3/ 9/48	2,777	...	679	...	...	...	...	....	23	..	..	3.75	0.2	3.55
		4/14/48	4,535	835	764	467	297	808	2,570	0.61	14	62	16	5.9	0.1	5.8
		5/13/48	4,864	764	969	656	313	1,135	2,652	0.67	18	60	13	4.4	0.3	4.1
T. B.	2½	12/ 5/47	1,506	430	365	255	110	440	525	0.70	16	44	25	...	...	...
		1/27/48	1,045	233	248	167	81	288	443	0.67	N	75	7	5.6	1.8	3.8
		2/17/48	615	175	93	62	31	107	302	0.66	N	N	N	8.2	3.2	5.0
		5/19/48	762	194	138	100	38	173	349	0.72	N	100	N	6.6	3.0	3.6
D. B.	4½	2/11/48	2,739	632	888	604	283	1,046	778	0.68	32	30	20	...	...	...
		3/31/48	2,316	556	970	733	237	1,268	255	0.75	46	7	20	4.8	0.3	4.5
		6/ 9/48	2,123	528	779	566	213	979	408	0.72	40	18	20	4.3	0.8	3.5
A. F.	9½	11/18/47	2,055	610	615†	498†	216†	861†	368‡	0.80	29	18	30	...	...	...
		2/11/48	2,910	660	422	189	233	327	1,690	0.45	8	67	20	...	...	...
		3/ 9/48	2,429	577	625	405‡	220†	700‡	932	0.65	22	44	20	3.5	0.4	3.1
		4/14/48	2,515	470	607	412	195	713	1,137	0.67	21	52	14	3.7	0.4	3.3
		5/ 5/48	1,877	683	534	361	173	624	397	0.67	25	23	40	3.3	0.4	2.9
		5/19/48	1,747	428	479	331	148	573	598	0.69	25	43	20	3.4	0.4	3.0
D. G.	4	11/18/47	1,524	520	385	231	154	399	476	0.60	20	39	35	...	...	...
		1/20/48	2,430	590	740	512	228	886	726	0.69	30	33	21	...	...	...
		2/17/48	1,401	363	390	297	94	514	588	0.76	22	56	20	6.3	1.1	5.2
		3/31/48	2,201	201	820	608	...	...	...	....	37	37	N	...	...	...
		5/ 5/48	1,218	406	288	190	98	329	380	0.66	13	43	33	3.8	0.2	3.6
		5/19/48	2,325	602	679	474	205	820	697	0.69	28	34	23	3.2	0.2	3.0
H. G.	3	1/20/48	1,228	303	305	194	111	335	479	0.63	16	60	16	...	...	...
		3/ 9/48	815†	55†	235	162	72	280	408	0.69	N	100	N	...	...	...
		4/14/48	2,500	590	738	516	222	893	795	0.69	27	34	20	5.0	1.0	4.0
		6/ 2/48	1,283	383	367	249	118	430	355	0.67	21	30	25	5.3	1.2	4.1
C. S.	4	11/18/48	.....	...	483	339	144	586	1,060	0.70	..	..	..	...	...	...
		1/20/48	.....	...	435	312	143	540	1,762	0.68	..	..	..	...	...	...
		2/17/49	2,847	367	328	216	112	373	1,995	0.66	6	58	7	4.8	0.2	4.6
		3/31/49	2,300	130	760	543	217	939	1,014	0.71	32	52	N	4.6	0.1	4.5
W. W.	5	3/31/48	1,685	375	555	405	150	701	459	0.71	30	30	16	4.4	1.05	3.35
E. K.‖	4½	10/16/41	1,885	375	860	575	285	975	250	0.67	50	8	8	...	...	...
		1/19/42	2,610	510	1,045	775	270	1,340	465	0.74	42	17	15	...	...	...
		3/ 3/42	6,800	785	2,020	1,170	850	2,025	3,150	0.58	29	50	10	...	...	...
		3/19/42	5,435	940	1,445	775	670	1,320	2,506	0.54	25	50	14	...	...	...
		4/ 3/42	3,100	670	935	600	335	1,040	1,055	0.64	27	50	18	...	...	...
		5/22/42	5,550	970	1,660	995	665	1,720	2,165	0.60	29	40	15	...	...	...
		6/12/42	5,185	850	1,610	1,035	575	1,790	1,970	0.64	30	39	14	...	...	...
		6/10/43	1,435	370	610	450	160	780	125	0.73	50	..	12	...	...	...
Normal**			620	190	210	140	70	...	120**	0.70	..	..	..	7.0	3.77	3.24

* N. indicates normal; 0+, very slight; t., trace; mo., moderate; in., increasing; r., rare; f., few; m., "many"; oc., "occasional."
† Probably somewhat low.
‡ Probably somewhat high.
§ Measles complicated by severe bronchopneumonia, total duration 1/29/48-2/24/48.
‖ Patient with severe nephrosis from earlier study.[15]
¶ Hematuria was microscopic.
# Per high power field.
** Footnote 12.

patients were hospitalized throughout the period of study in the nephritic service of the children's division of Cook County Hospital. They were treated by the usual methods, with the addition of choline and methionine,[5] given as indicated in table 1.

The following lipids were determined: total lipid, phospholipid, total cholesterol, ester cholesterol,[6] free cholesterol, cholesterol ester[6] and neutral fat.[6] The Bloor technic was used to prepare alcohol-ether plasma extracts, aliquots of which were analyzed for acetone-soluble lipid and phospholipid by Bloor methods[7] and for cholesterol by Sperry-Schoenheimer methods.[8]

5. Eli Lilly & Company, P. O. Box 618, Indianapolis 6, supplied the choline and methionine.

6. Calculated values.

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*ues and Clinical Data on Nine Patients with Nephrosis**

Serum Proteins, Gm./100 Cc.			Therapy, Dose in Gm.		Clinical Data			Laboratory Data			
Alpha Globulin	Beta Globulin	Gamma Globulin	Duration, Mo.	Choline	Methionine	Edema	Weight, Lb.	Lowest Recorded Weight	Albuminuria	Hematuria	Nonprotein Nitrogen, Mg./100 Cc.	Complications
....	....	....	6	2	2	0-1+	20	19	3-4+	0	..	Mild cough
0.63	....	....	7	1.5	1.5	4+	29	..	11 Gm.	1+	34	.....
....	....	....	8	1.5	1.5	2+	31	..	12 Gm.	2+	47	Glycosuria, trace
0.6	3.35	0.15	9	1.5	1.5	3+	34-35	..	10 Gm.	1+	47	Glycosuria, trace
....	....	....	4	...	...	2-4+	36	28	4+	0	40	Pleural effusion
0.9	....	....	5	...	...	2+	28½	..	0	0	..	Measles, 1/19/48-1/26/48
1.6	....	....	6	1.5-2	1.5-2	0	28-29	..	0-1+	0	..	Fever, origin (?)
1.4	1.25	0.95	9	1.5	1.5	0	32½	..	2+	0	..	Pertussis, 5/13/48
....	....	....	3	1.5	1.5	1+	46	..	2-3+	0+	32	.....
....	....	....	4	1.5	1.5	1+	44-45	..	2+	0+	32	Chickenpox, 4/1/48
1.4	1.55	0.25	7	1.5	1.5	1+	47	..	2+	0+	26	.....
....	....	....	3	...	...	2-3+	63	55	2-4+	0+	..	Pneumonitis
....	....	....	11	1.5	1.5	2+	..	..	4+	0+	41	Acute nephritis (?)
0.52	....	....	12	1.5	1.5	1-2+	70	..	16-19 Gm.	0+	40	.....
....	....	....	13	1.5	1.5	3+	73	..	40 Gm.	0+	41	Glycosuria, trace
0.85	1.9	0.15	14	1.5	1.5	2+	70	..	17 Gm.	0+	..	Glycosuria, trace
1.0	1.9	0.1	14	1.5	1.5	4+	74	..	3+	0+	..	Glycosuria, trace
....	....	....	2	...	...	2-4+	40	30	4+	0	..	.....
....	....	....	4	...	...	0-1+	35	..	2-3+	2+	..	.....
1.4	....	....	5	2.0	2.0	1-2+	37-30	..	T.-3+	0	27	.....
....	....	....	6	1.5	1.5	1+	37	..	18 Gm.	4+	..	Glycosuria, 1+
1.05	2.4	0.15	8	1.5	1.5	2+	37-40	..	3-4+	4+	..	Slight glycosuria
1.1	1.8	0.1	8	1.5	1.5	2-3+	41	..	4+	3+	34†	Peritonitis
....	....	....	2	...	...	2+	37	31	3-1+	0	22	Measles, 1/16/48-1/26/48
....	....	....	4	1.5	1.5	1-2+	32-35	..	3+	0+	..	Slight fever
....	....	....	5	1.5	1.5	1+	31-33	..	1-3+	0+	27†	Slight fever, (?) cause
1.2	1.3	1.6	7	1.5	1.5	1+	36	..	2-3+	0+	..	Peritonitis
....	....	....	11	...	...	1-2+	40	34	3-4+	0	..	Pneumonia, 1/30/48-12/26/48
....	....	....	13	...	...	2-3+	36-40	..	3-4+	1+	40†	.....
1.8	....	....	14	1.5-2	1.5-2	1+	35-36	..	2-3+	2+	..	Measles, 1/29/48-2/24/48§
....	....	....	15	1.5	1.5	1-2+	38	..	3+	0	32	.....
....	....	....	13	1.5	1.5	0	42-43	41	2-3+	1+	40	Measles, 1/25/48-1/29/48
....	....	....	2	...	...	Mo.	..	..	3+	0	28	Recent cellulitis
....	....	....	5	...	...	In.	..	..	3-4+	R.¶	35	Peritonitis (?)
....	....	....	7	...	...	In.	..	..	4+	F.	40-26	None
....	....	....	7	...	...	In.	..	..	2-4+	F.	50-34	None
....	....	....	8	...	...	Mo.	..	..	3+	M.	..	Dyspnea; rales
....	....	....	9	...	...	In.	..	..	3-4+	Oc.	..	None
....	....	....	10	...	...	In.	..	..	4+	7#	33	None
....	....	....	22	...	...	0	..	..	...	..	..	.....
1.1	1.2	0.94	..	...	...	.....	..	..	...	..	25-35	.....

All protein determinations were made in the department of biochemistry of the Michael Reese Hospital.[9] The total serum protein was estimated by a conventional biuret technic. Fractional proteins were determined by a chemical fractionation technic[10] which yields results comparable with electrophoresis. Total albumin,[11] total globulin, alpha globulin, the combined beta + gamma globulin fraction and in a number of instances separate beta globulin and gamma globulin fractions were estimated.

RESULTS

In table 1 are summarized all the total and fractional lipid and protein values together with the patients' clinical status at the time of each determination. Average normal lipid and protein values are included.[12]

9. Dr. Clarence Cohn, Director of the Laboratory, supervised the protein determinations.

10. Wolfson, W. Q.; Cohn, C.; Calvary, E., and Thomas, E. M.: J. Lab. & Clin. Med. **33**:1276, 1948. Wolfson, W. Q.; Cohn, C.; Calvary, E., and Ichiba, F.: Am. J. Clin. Path. **18**:723, 1948.

11. This technic yields lower albumin values than the conventional clinical technic of Howe, since the latter includes alpha globulin in the "albumin" value.

12. As determined on 24 normal children (Thomas, E. M.: Total and Fractional Blood Lipid Levels in Diseases of Childhood, Am. J. Dis. Child. **74**:563 (Nov.) 1947). Wolfson and others.[10]

COMMENT

We shall review briefly (1) characteristics of the plasma lipid patterns and their relation to other nephrotic symptoms during the course of the disease and (2) evidences of correlation between lipid levels and protein levels.

Lipid Patterns.—Total and fractional lipid levels varied from case to case; they also fluctuated markedly in individual cases, being highest during periods of severe clinical activity. No relation between the total duration of the disease and the degree of lipid elevation was apparent. The maximum total lipid level obtained in this group of cases was 4,800 mg. per 100 cc. (average normal, 620 mg. per 100 cc.).

Whenever the total lipid level was high, all constituent fractional lipid levels were usually elevated, though not to the same degree. Neutral fat showed the greatest increase over normal and accounted for a greater percentage of the total lipid increase than did either cholesterol or phospholipid in at least half of the determinations. Furthermore, ratios of neutral fat to total lipid, total cholesterol and phospholipid were, in most cases, abnormally high,[13] whereas ratios of cholesterol and phospholipid to the total lipid and to each other were normal.

The ratio of ester to total cholesterol was within or near the normal range in most determinations. This agrees with Gottfried's findings [14] but differs from the observations in a case previously reported,[15] in which the ratio of ester to totol cholesterol appeared to decrease during severe phases of the nephrotic syndrome.

Relation of Lipid Levels to Other Nephrotic Symptoms.—Edema: Though the patients with the highest lipid levels showed severe edema, edema occurred also when lipid levels were much less elevated; also, high lipids levels were obtained when edema was minimal. There was thus no close correlation between occurrence of edema and elevation of the blood lipids in these cases.

Albuminuria: With but one exception, marked albuminuria was present whenever lipids were elevated.

Hypoproteinemia: In view of the contention that lipemia in the nephrotic syndrome may be secondary to hypoproteinemia, attention is directed to the cases of A.A., A.F. and D.G. (table 1) in which lipemia occurred when total protein levels were essentially normal.

Effect of Measles on the Lipid Pattern.—In four patients (T.B., H.G., C.S. and W.W.) measles developed during the course of the nephrotic syndrome.

In one of these patients (T.B.) the total lipid level fell from high to nearly normal immediately after the attack and was still nearly normal four months after the attack. Phospholipid and cholesterol underwent the greatest reduction; neutral fat showed little change. Coincident with the plasma lipid fall, edema, albuminuria

13. On the other hand, the ratio of phospholipid to neutral fat was abnormally low. Since the hyperlipemic serum of nephrosis is characteristically milky, the occurrence of a low ratio of phospholipid to neutral fat is of interest in view of the suggestion in an article by Stearns and co-workers (*New England J. Med.* **238**:16, 1948) that visible lipemia may depend on hyperlipemia associated with a relative decrease in phospholipids, which normally maintain other fats in a supersaturated state in the serum.

14. Gottfried, S. P.; Steinman, J. F., and Kramer, B.: Chemical Studies in Children with Nephrotic Syndrome, Am. J. Dis. Child. **74**:283 (Sept.) 1947.

15. Thomas, E. M.: Total and Fractional Blood Lipid Levels in the Nephrotic Syndrome, Am. J. Dis. Child. **65**:770 (May) 1943; Total and Fractional Blood Lipid Levels in Diseases of Childhood, ibid. **74**:563 (Nov.) 1947. (We have used this case report in our present data [patient E. K.].)

and hypoproteinemia improved, and the improvement lasted at least three months after the measles.

In two other patients (C.S. and W.W.) no lowering of lipids was observed after measles. Changes in the other nephrotic symptoms were slight.

Relations of Lipid Levels to Protein Levels.—By chemical analysis of electrophoretically separated serum protein fractions Blix and co-workers,[4a] showed that the serum albumin and globulins all contain phospholipid and cholesterol. When the total quantity of these lipids thus bound to protein in normal blood is estimated from the figures of Blix and co-workers, the resulting value, approximately 500 mg. per 100 cc., is equivalent to about three-fourths of the normal total lipid of the blood (table 2). If so much of the blood lipid is combined with the blood protein, it seems conceivable that changes in the lipid levels may depend on, and hence should show correlations with, changes in the protein levels.

Our data were therefore examined for evidences of correlation between the lipid and protein levels.

Relations of Lipid Levels to Levels of Total Protein, Albumin and Globulin.—When lipid levels were plotted against corresponding protein levels in the group as

TABLE 2.—*Relation of Lipid Levels to Protein Levels*

Protein Fraction	Normal Value, Gm./100 Cc.	Cholesterol Plus Phospholipid in Protein, Percentage *	Estimated Total Cholesterol Plus Phospholipid in Protein, Mg./100 Cc.
Albumin	3.77	3.3	124
Alpha globulin	1.1	11.7	129
Beta globulin	1.3	18.7	224
Gamma globulin	0.94	1.4	13
Total	....	....	490

* Blix, G.; Tiselius, A., and Svensson, H.[4a] Per cents of cholesterol and of phospholipid as given by Blix and co-workers are added together here.

a whole, the total lipid, total cholesterol and neutral fat levels showed no correlation with total globulin (chart 1 *A*, *B* and *C*). Lipid levels showed no correlation with total protein levels.

There was, however, a generally inverse correlation between the levels of these lipids and the total albumin level (chart 1 *D*, *E* and *F*). In most instances albumin levels were very low, ranging from 3 per cent to 15 per cent of normal, and in every such instance of low albumin the lipids were elevated; in the one patient whose serial determinations demonstrated a rise in albumin from a low level to normal the corresponding total and fractional lipid levels fell from high to normal and below. Cholesterol, in particular, fell to 50 per cent of normal (table 1, patient T. B.).

From table 1 it appears that six of the eight gamma globulin levels determined in this study were very low and that in each of the six the total and fractional blood lipid levels were elevated. On the other hand, the lipid levels of the two patients with normal gamma globulin levels were, respectively, normal and elevated slightly. Other investigators [16] have noted low gamma globulin levels in nephrosis. Wolfson

16. Addis, T.: Glomerular Nephritis: Diagnosis and Treatment, New York, The Macmillan Company, 1948, p. 216. Wolfson and others.[10]

and co-workers,[10] in a study of nephrotic plasma protein levels in a group which included the patients reported here, observed correlation between gamma globulin and albumin levels, both being low.

Relations of Lipid-Protein Ratios to Lipid Levels and to Protein Levels.—When lipid levels and protein levels were plotted against corresponding lipid-protein ratios in the group as a whole, the following relations were noted (glyceride equals neutral fat): 1. Cholesterol: albumin ratios and neutral fat: albumin ratios showed a generally inverse correlation with total albumin levels (chart 2 *A* and *B*) and a generally direct correlation with cholesterol and neutral fat levels respectively

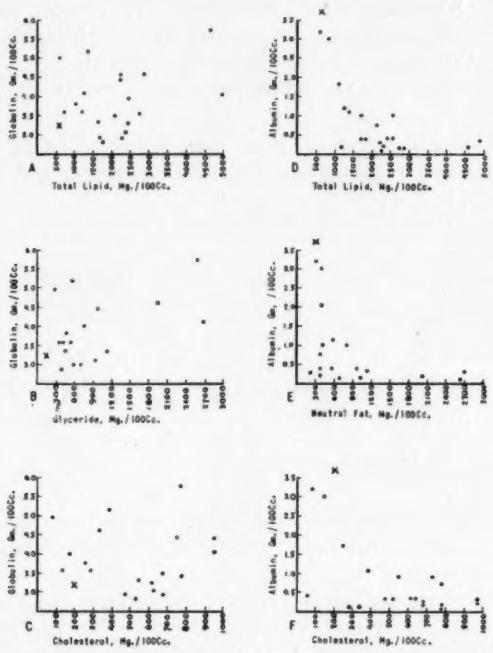

Chart 1.—Relations of lipids to albumin and to globulin: *A*, total lipid and globulin; *B*, neutral fat and globulin; *C*, cholesterol and globulin; *D*, total lipid and albumin; *E*, glyceride and albumin; *F*, cholesterol and albumin. (*X* indicates normal; glyceride equals neutral fat.)

(chart 2 *C* and *D*). 1. Cholesterol: globulin ratios and neutral fat: globulin ratios showed no relation to total globulin levels (chart 3 *A* and *B*) and a generally direct correlation with cholesterol and with neutral fat levels respectively (chart 3 *C* and *D*).

With due allowance for the limited number of determinations represented, the above observations suggest that the blood levels of cholesterol and of neutral fat in these patients (1) may be correlated with the albumin levels and with the gamma globulin levels and (2) may depend in part on the quantity of these lipids associated with albumin, and perhaps also with globulin.

The results indicate that further investigation of the relations is needed.

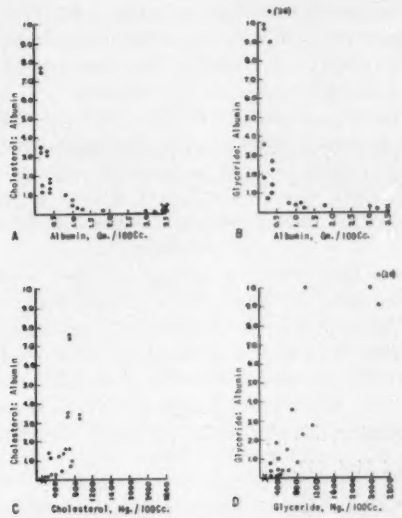

Chart 2.—Relations of lipid : protein ratios to proteins and to lipids: *A*, cholesterol : albumin and albumin; *B*, glyceride : albumin and albumin; *C*, cholesterol : albumin and cholesterol; *D*, glyceride : albumin and glyceride. (*X* indicates normal; glyceride equals neutral fat.)

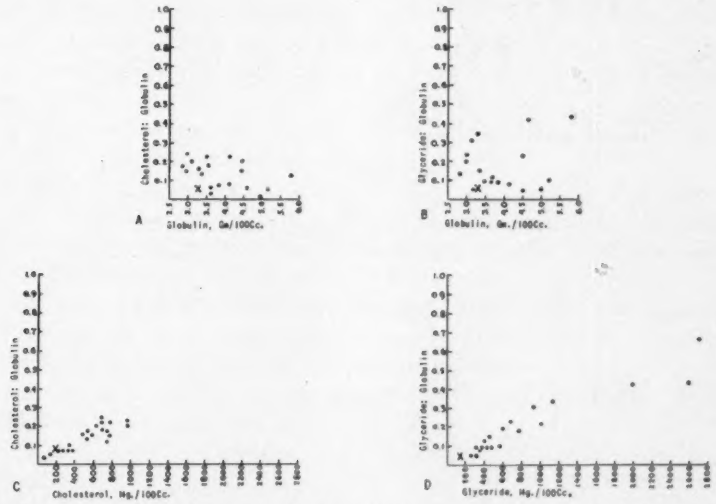

Chart 3.—Relations of lipid : protein ratios to proteins and to lipids: *A*, cholesterol : globulin and globulin; *B*, glyceride : globulin and globulin; *C*, cholesterol : globulin and cholesterol; *D*, glyceride : globulin and glyceride. (*X* indicates normal; glyceride equals neutral fat.)

SUMMARY

Postabsorptive total and fractional plasma protein and plasma lipid levels were determined at intervals over a three to six month period in eight children, aged 2 to 10 years, with nephrotic lipemia. The data thus obtained and the clinical features present at the time of the determinations are tabulated.

It was observed that in most patients all fractional lipid levels were elevated but that the elevation of neutral fat tended to be disproportionately great. The ester cholesterol : total cholesterol ratios were predominantly normal.

On these patients there was no correlation of total or fractional blood lipid levels with the levels of total protein and total globulin and probably none with alpha globulin.

There was evidence for correlation between the lipid levels and the levels of albumin and of gamma globulin. There was also some evidence for correlation of the lipid levels with the lipid : albumin and lipid : globulin ratios.

The need for further investigation of the above described relation is indicated.

Attention is directed to the presence of mild glycosuria in several of these cases (table 1). In such cases, blood sugar and glucose tolerance tests are indicated, to aid in determining whether this glycosuria is of renal or metabolic origin.

651 South Brentwood Blvd. (5).

A PLAN FOR THE PERMANENT ORGANIZATION OF THE INTERNATIONAL PEDIATRIC ASSOCIATION

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ROCHESTER, MINN.

UP TO THE present, the International Pediatric Association has functioned as an organization to hold a congress every three years with the following aim: "The bringing together of the doctors in all countries who are concerned with the diseases of children." This is a rather narrow view to take of pediatrics at present in that it leaves entirely out of account the whole field of preventive pediatrics, the prevention of physical disease and, in its even broader aspects, the prevention of the mental, emotional and social disturbances of childhood. It would seem that the International Pediatric Association should widen its horizon and state categorically that, in the future, its purposes shall be (1) to aid in every way possible in the prevention and cure of the physical, mental and emotional disorders of children and (2) to promote world peace by helping, through adequate child care, to raise up a generation of mature adults.

In order to accomplish these purposes, it is essential to:

1. Develop a permanent organization which will further the exchange of information and ideas on all matters of interest to the pediatrician

2. Promote closer relationships among the pediatricians in the various countries of the world

3. Study and improve the standards of pediatric education and stimulate the exchange of pediatric teachers and students

4. Hold an International Congress every three years in cooperation with the Bureau for the Coordination of International Congresses of Medical Sciences in order to attain maximum attendance and with every possible use of the Congress membership for clinics, lectures and discussion groups

5. Cooperate with the World Health Organization, the Food and Agriculture Organization, the International Children's Emergency Fund and the Educational, Scientific and Cultural Organization of the United Nations

6. Give aid in the field of child care to other related organizations in their international and regional meetings

7. Call regional and international conferences for specific purposes of study and discussion

From this outline of the possible objectives it is evident that our present Congress has already achieved some of them. Looking at our program, we see that

Read before the Sixth International Congress of Pediatrics, Zurich, Switzerland, July 24 to 28, 1950.

we are studying pediatric education in many countries. The reports of Dr. Wallgren and Dr. Weech on pediatric education are the first of many studies that will be necessary before the entire field is covered. Having determined the requirements of staff, equipment, hospital beds and research facilities, what can be done internationally to help countries acquire them? This Congress, in its development of courses of lectures and demonstrations, in its exhibits which will be available for a time before and after the meeting of the Congress, in its time relation to other congresses, is of educational importance far beyond that of previous ones. This is but a start. I feel sure that succeeding congresses will make contributions far exceeding those which, in the past, we have thought possible for international gatherings.

Since the last Congress, the World Health Organization has lost its interim status and become a full fledged member organization of the United Nations. It concerns us directly that the Maternal and Child Health Division was set up as one of its major priorities in international work. Dr. Martha M. Eliot, until recently the Associate Director of the Children's Bureau of the United States, is now the Assistant Director General of the World Health Organization. She brings to the work of the Maternal and Child Health Division knowledge which will give great impetus to international pediatrics. Here we have an opportunity to offer the World Health Organization our earnest cooperation at the international as well as the national level. Dr. Eliot will speak to us at this meeting and will probably outline the mode of attack on a few of the many problems which face us in the international field.

The United Nations International Children's Emergency Fund, organized primarily to feed the starving children of Europe after the United Nations Relief and Rehabilitation Administration stopped functioning, has carried its work to other continents of the world as well. In cooperation with the World Health Organization, the Food and Agriculture Organization, the Scandinavian Red Cross Organization and the Don Suisse, it has accomplished much in the prevention of disease, improvement of nutrition and pediatric education. With the termination of the activities of U.N.I.C.E.F., the responsibility of carrying on this large medical program will fall for the most part on the Maternal and Child Health Division of the World Health Organization and our support will be even more essential. It seems important, therefore, that at this Congress a committee be appointed to cooperate with the United Nations' health organizations and that it be so selected geographically that it will be possible for it to meet without too great expense to the Association to discuss and work out common health problems.

The second objective in our constitution, as it has been drawn up, is to promote peace by helping to raise up a generation of mature adults. I hope that you will allow me to digress for a few moments to tell you why that was put in and why it is so important that we as pediatricians play a major role in this program.

Until 1900 the main sphere of medicine was considered to be the care of the sick, and in some areas today it is still so considered. This was the period in which the treatment of disease was regarded as the entire function of the physician. Since 1900, however, a feeling has developed not only that the role of the physician is the cure of physical disease but also that disease prevention is possibly of equal or even greater importance. The reduction in the high infant mortality rates

during the first half of the twentieth century is one of the outstanding accomplishments of preventative medicine. The decrease of certain contagious diseases through vaccination and the control of water and milk supplies and other public health measures has brought about a situation in which in recent years accidents have become the most frequent cause of death in the age group from 0 to 15 years in the United States. In this second period of medicine we considered that physical health was an end in itself and that the saving of life by the prevention or cure of disease was the sum total of a physician's duty.

We come now to a third period in which health is being considered in a much broader framework. The World Health Organization has defined health as a "state of complete physical, mental and social well-being and not merely the absence of disease or infirmity." President Hoover of the United States of America, in his address to the White House Conference on Child Health and Protection in 1930, stated that the health of children is more than just physical health; it is, in addition, the mental, emotional and spiritual health of children in which we are interested. The contributions in the fields of growth and development, of mental hygiene and preventive psychiatry have added much to our knowledge of child care in the last decade. Studies such as are going on in the Rochester Child Health Institute, started under the leadership of the late Dr. C. Anderson Aldrich in 1944, have been pioneering in the application of this new knowledge to the care of all the children in the community.

In this third stage of medical care, the pediatrician has broadened his responsibility over and above the child's physical care to interest himself in the mental, emotional and social growth and development of the child. It is envisioned that the realization of this aim will show effects beyond the period of childhood, inasmuch as it will result in a larger number of persons becoming responsible and cooperating citizens, more capable of living in peace with one another both nationally and internationally. This field has recently received a tremendous stimulus in the United States of America where the Midcentury White House Conference on Children and Youth, basing its concern for children on the primacy of spiritual values, democratic practice and the dignity and worth of every individual, stated that "the purpose of the conference shall be to consider how the mental, emotional, and spiritual qualities essential to individual happiness and responsible citizenship can be developed in children and what physical, economic, and social conditions are deemed necessary to this development." In this process of the child's growth to maturity, the physician, and particularly the pediatrician, has an important role to play that, in its successful accomplishment, would quite outrank any of the benefits that he has brought to humanity thus far.

As Dr. George Brock Chisholm, the Director General of the World Health Organization of the United Nations, has said:

> Only when a generation of children has successfully reached this state of adult maturity, can we hope to have enough people able to see and think clearly enough to be able to prevent the race going on as we have gone from slaughter to bigger and better slaughter.

This is a great challenge to the pediatricians of the world; let us hope that we have the wisdom and the time necessary to meet this challenge.

RELATION OF HOMOLOGOUS SERUM HEPATITIS TO PROPHYLACTIC INJECTION OF HUMAN BLOOD FRACTIONS

A Study of 13,755 Cases with Injections

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THE RECOGNITION of homologous serum hepatitis as a separate entity focused the attention of the members of the medical profession on the causal relation which exists between this disease and the administration of human blood and plasma. Reports have appeared sporadically in the medical literature of patients in whom hepatitis had developed after their inoculation with some form of human plasma. Hirsch,[1] in 1885, described an outbreak of jaundice in a Bremen shipyard among 1,289 workers vaccinated with glycerinated human lymph. Jaundice developed in 191 adults after an incubation period of several weeks or months. In two other groups, of 87 and 500 adults respectively, inoculated with vaccine from a different batch jaundice did not develop. In 1938, Propert [2] reported on a series of seven children to whom 4.5 cc. of measles immune serum (human) was given subcutaneously. Three months later, all seven became jaundiced, and three died. MacNalty [3] reported on 100 children who received measles immune serum from the same pool, in 37 of whom jaundice developed and seven of whom died. In March 1942, each of 266 British soldiers was given less than 14 cc. of pooled mumps convalescent plasma intramuscularly,[4] and jaundice developed in 86 men. Among 36 others who received pooled serum, eight cases of jaundice appeared.

These reports might have received scanty attention had it not been for the tremendous incidence of jaundice which developed in service personnel who had received injections of yellow fever vaccine. Findlay and MacCallum [5] had expressed

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From the pediatric services of Dr. Louis H. Barenberg at the Morrisania City Hospital and the Jewish Memorial Hospital.

1. Hirsch, A.: Handbook of Geographical and Historical Pathology, translated from the German, ed. 2, by C. Creighton, London, New Sydenham Society, 1883-1886, vol. 3.

2. Propert, S. A.: Hepatitis After Prophylactic Serum, Brit. M. J. **2**:677 (Sept. 24) 1938.

3. Ministry of Health: On the State of the Public Health: Annual Report of the Chief Medical Officer of the Ministry of Health for the Year 1937, London, His Majesty's Stationery Office, 1938.

4. Beeson, P. B.; Chesney, G., and McFarlan, A. M.: Hepatitis Following Injection of Mumps Convalescent Plasma: Use of Plasma in the Mumps Epidemic, Lancet **1**:814 (June 24) 1944.

5. Findlay, G. M., and MacCallum, F. O.: Note on Acute Hepatitis and Yellow Fever Immunization, Tr. Roy. Soc. Trop. Med. & Hyg. **31**:297 (Nov.) 1937.

the belief that some relation existed between the human plasma in the yellow fever vaccine and the appearance of jaundice. Fox [6] had reported from Brazil a high incidence of jaundice among persons vaccinated with yellow fever vaccine. The investigations of Sawyer [7] in 1944 clearly demonstrated that the etiological agent of the hepatitis was in the human plasma; when the plasma was replaced by saline solution the incidence of the disease fell off completely. The same relation seemed to be present in the Russian study of pappataci fever wherein human plasma was used in the vaccine.[8] However, when other cases of homologous serum hepatitis began to appear, it became apparent that the pooled plasma, which was being used extensively for the treatment of shock in war injuries, contained the responsible factor.

The steady rise in the incidence of homologous serum hepatitis became a source of great concern to my associates and me at the Morrisania City Hospital. Since 1934 we had employed blood fractions intramuscularly to prevent the development and spread of certain contagious diseases in the medical pediatric ward. Each child over 3 months of age received 30 cc. of pooled plasma on admission, and injection of this amount was repeated if the patient remained in the hospital for six weeks or more during the spring or if a primary case of measles or German measles developed in the ward. The rationale of this procedure basically was to prevent the development of secondary cases of measles. In the first report from the hospital [9] it was pointed out that many cases of primary measles were either attenuated or possibly aborted if plasma was given early during the incubation period. It was also observed that German measles responded in a similar manner, and the occurrence of scarlet fever and mumps had possibly been lessened. The incidence of primary and secondary cases of measles in our medical pediatric ward was compared with the incidence of cases in the surgical pediatric ward in our hospital and the medical pediatric wards of two other city hospitals which serve the same type of population.[10] This comparison revealed that the patients in our ward had a much lower incidence of primary measles, and that there was a complete absence of secondary measles, in contrast to the patients with whom comparison was made. It should be noted that in the other city hospitals some kind of prophylaxis was occasionally used, although not as constantly as in our medical ward.

In view of the benefits derived from this prophylactic procedure, there was considerable reluctance to abandon it. On the other hand, it would be unfair to expose any child to the hazards of hepatitis, a disease which was so apparently transmitted by infected plasma, serum or blood. Accordingly, in 1946 a preliminary check was made of all the patients with jaundice who had been admitted to the hospital since introduction of this procedure in 1934. Analysis revealed that

6. Fox, J. P.; Manso, C.; Penna, H. A., and Pará, M.: Observations on the Occurrence of Icterus in Brazil Following Vaccination Against Yellow Fever, Am. J. Hyg. **36**:68 (July) 1942.

7. Sawyer, W. A.; Meyer, K. F.; Eaton, M. D.; Bauer, J. H.; Putnam, P., and Schwentker, F. F.: Jaundice in Army Personnel in the Western Region of the United States and Its Relation to Vaccination Against Yellow Fever, Am. J. Hyg. **39**:337 (May) 1944.

8. Sergeiev and others, cited by Sawyer.[7]

9. Barenberg, L. H.; Greene, D., and Grand, M. J. H.: Prophylactic Use of Parental Blood Serum Against Contagion in a Pediatric Ward, Am. J. Dis. Child. **57**:322 (Feb.) 1939.

10. Barenberg, L. H.; Levy, W.; Greenstein, N. M., and Greenberg, B.: Prophylactic Use of Human Serum Against Contagion in a Pediatric Ward, Am. J. Dis. **63**:1101 (June) 1942.

there was not one patient during the entire 12 year period who had received plasma from one to six months prior to admission and therefore whose jaundice could fall into the category of homologous serum hepatitis. These findings encouraged us to continue the administration of pooled plasma and to use gamma globulin when available. Naturally, the patients were carefully scrutinized with regard to any manifestations of hepatitis, with or without jaundice, if they were readmitted to our hospital or to either of the other two city hospitals.

MATERIAL

The material studied was divided into three groups.

1. In the first group were included all children 3 months to 12 years of age who were admitted to the four hospitals studied over a 15 year period and all patients with jaundice observed during this time. All children admitted to the Morrisania City and Jewish Memorial Hospitals received inoculations. From 1934 to 1938 an injection of 30 cc. of pooled parental serum was used on admission exclusively. Blood was taken from the parents of admitted children. It was allowed to stand at room temperature until a clot formed and then was refrigerated. The serum was separated and tested for syphilis, and Wassermann-negative serum was pooled. From 1938 to 1945 blood plasma from the hospital blood bank was employed, and from 1945 to the present dried and reconstituted plasma from Red Cross stocks was used. Gamma globulin was provided at times from 1947 to the present by the New York City Department of Health. The amount used (2 cc.) was considered equivalent to 30 cc. of plasma.

From Jan. 1, 1934 to Dec. 31, 1949 a total of 11,447 children from 3 months to 12 years of age received one of these forms of prophylaxis on admission to the Morrisania City Hospital. From Jan. 1, 1944 to Dec. 31, 1949 a total of 2,308 children from 3 months to 12 years of age were admitted to the pediatric service of the Jewish Memorial Hospital. Pooled plasma from the hospital blood bank was administered to the children in exactly the same manner as at Morrisania City Hospital.

2. The second group comprised all the patients with jaundice admitted to the four hospitals investigated. A comparison was made between those children who had previously been inoculated and those who had not. The relation of the development of jaundice to the interval between the inoculation and the appearance of jaundice was studied.

3. The third group consisted of 22 nonicteric children who were readmitted to the Morrisania City Hospital from 1946 to 1949 with symptoms of gastrointestinal disturbance including anorexia and light colored stools and who had previously been admitted to the hospital 50 to 100 days before. These children were studied to determine whether they had hepatitis without jaundice, and the following liver function tests were performed: cephalin flocculation, serum bilirubin, sulfobromophthalein sodium retention and determinations of urinary bile and urobilinogen.

FINDINGS

Table 1 indicates that the incidence of jaundice in four active pediatric services was rather small, in keeping with the generally accepted idea that hepatitis is not common in children, with the exception of occasional epidemics which are found in child care institutions. Only 120 cases occurred in a total of 41,353 children admitted between the ages of 3 months and 12 years. Horstmann [11] has pointed out that hepatitis occurs sporadically, as a rule, and that the disease is much milder in children than in adults.

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11. Horstmann, D. M.; Havens, W. P., Jr., and Deutsch, J.: Infectious Hepatitis in Childhood, J. Pediat. **30**:381 (April) 1947.

Table 2 reveals that jaundice was less frequent among children who had received previous injections than in children who had not received injections, suggesting that the injections had had no untoward effect—109 cases were found among noninoculated children, whereas only 11 patients became ill with hepatitis after inoculation. Of the 11 patients who became jaundiced, only two acquired the condition less than two years after injection, and the other nine acquired it on an average of 6½ years following injection. One is inclined to believe that the injection itself may have had a protective effect.

Many of the patients who had received injections at the Morrisania City Hospital were subsequently admitted for various conditions to the other city hospitals. None of the patients with jaundice in Fordham or Lincoln Hospitals had received injections at Morrisania City Hospital or any other hospital.

TABLE 1.—*Incidence of Jaundice in Hospital Admissions Among Children Aged 3 Months to 12 Years, 1934 to 1949*

	Morrisania City Hospital	Jewish Memorial Hospital *	Fordham Hospital	Lincoln Hospital	Total
Total admissions	11,447	2,309	13,486	14,112	41,353
Total cases of jaundice	33	2	49	36	120

* 1944 to 1949.

TABLE 2.—*Comparison of Incidence of Jaundice in Children Who Received and Those Who Did Not Receive Intramuscular Human Plasma, Serum or Gamma Globulin*

	Total	Morrisania City Hospital	Jewish Memorial Hospital	Lincoln Hospital	Fordham Hospital
I. Children who did not receive previous inoculation	109	24	1	49	35
II. Children who received previous inoculation	11	9	1	0	1
A. Children who received injections more than 1 year before onset of jaundice	11	9	1	0	1
B. Children who received injections less than 1 year before onset of jaundice	0	0	0	0	0

The most significant feature of the findings is the fact that none of the patients who became jaundiced after injection had been inoculated less than one year before the jaundice appeared, and therefore not one could be considered as having homologous serum hepatitis. This period of one year was arbitrarily selected because it is considerably beyond the limit of the incubation period of this disease. The limit is usually up to 150 days.

In the group of 22 nonicteric children studied for possible hepatitis without jaundice, not one child showed evidence of hepatic dysfunction, as evidenced by normal results in all liver function and urine tests performed. This finding was not entirely unexpected, since in every one of the reported cases homologous serum hepatitis in children was associated with considerable jaundice.

COMMENT

It was found that in a total of 13,755 children who had received intramuscular injections of human plasma, serum or gamma globulin, not a single case of homologous serum hepatitis developed. It should be noted that many of these children

had also received blood and plasma intravenously as well during their hospital stay. In marked contrast to these results are the reports of cases in children which continue to appear in the pediatric literature.

A careful review of these cases suggests the possibility that certain factors are present which predispose toward the occurrence of the disease. The following are considered as possible predisposing factors: (1) age, (2) method of administration of plasma, (3) variation in the virulence of the etiological agent (virus) and (4) physical status.

1. *Age.*—Although there is an increasing awareness of the frequency of liver diseases in childhood, the incidence of homologous serum hepatitis is still much lower in children than in adults. The reason for this is not well understood, although studies of the various protein fractions of the blood suggest that the gamma globulin content in infants is proportionately higher than in adults.[12] Apparently the liver in a child, except under certain conditions, is less vulnerable to viral infections than that of an adult. During the years 1946 to 1949 a number of cases of homologous serum hepatitis occurred among adult patients at the Morrisania City Hospital. It was interesting to note that these adult patients had received the same Red Cross plasma which had been supplied to the pediatric ward for intramuscular administration.

Brightman and Korns [13] reported 29 cases of jaundice in a total of 649 patients who had received pooled plasma intravenously, and not one case occurred in the age group from birth to 19 years. Lehane [14] reported a series of 134 cases of post-transfusion (blood or plasma) hepatitis in a follow-up of cases from 1945 to 1948, and only one case was found in the age group up to 10 years. In a series of cases of post-transfusion hepatitis reported by McGraw [15] and by Ratnoff and Mirick,[16] the incidence of the condition in children was small.

Attention must be called to the fact that in many of the cases of homologous serum hepatitis which were reported in children the patients were infants who received blood or plasma when less than 3 months old. There were at least 10 cases in this age group, representing about a third of the total number reported. It should be remembered that none of our patients who received routine injections of plasma were in this age group.

2. *Method of Administration.*—In most of the cases of homologous serum hepatitis reported in children the patients had received plasma intravenously. On the other hand, cases have been described in which the subcutaneous injection of

12. Desmond, M. M.; Zimmerman, H. J.; Sweet, L. K., and Thomas, L. J.: Thymol Turbidity Values in the Sera of Newborn and Premature Infants and Mothers at Term, Pediatrics **3**:49 (Jan.) 1949.

13. Brightman, I. J., and Korns, R. F.: Homologous Serum Jaundice in Recipients of Pooled Plasma, J. A. M. A. **135**:268 (Oct. 4) 1947.

14. Lehane, D.; K. Kwantes, C. M. S.; Upward, M. G., and Thomson, D. R.: Homologous Serum Jaundice, Brit. M. J. **2**:572 (Sept. 10) 1949.

15. McGraw, J. J., Jr.; Strumia, M. M., and Burns, E.: The Incidence of Post-Transfusion Serum Hepatitis, Am. J. Clin. Path. **19**:1004 (Nov.) 1949.

16. Ratnoff, O. D., and Mirick, G. S.: Acute Hepatitis in General Hospital Practice: Role of Transfusions and Inoculations, Bull. Johns Hopkins Hosp. **83**:299 (Oct.) 1949.

human measles immune serum resulted in jaundice.[17] Thalhimer,[18] who reported on the extensive use of human measles immune serum, never mentioned the occurrence of homologous serum hepatitis. In fact, no cases were described in this country following the use of human measles immune serum.

All our patients were given plasma intramuscularly. In 1943 the Ministry of Health in Great Britain reported [19] that a total of 366 liters of pooled plasma from 3,000 donors was given intramuscularly to 36,000 recipients, and not one case of jaundice developed. As mentioned before, the same holds true for our series. There seems to be a difference in the results when there is a difference in the mode of administration of plasma. The adult patients at the Morrisania City Hospital in whom jaundice developed all received plasma intravenously. The impression that the etiological agent of homologous serum hepatitis is less likely to produce the disease in children when plasma is given intramuscularly awaits further clarification.

3. *Variation in Virulence of the Etiological Agent.*—Most of the cases of homologous serum hepatitis were reported during the years 1942 to 1945, at the time when great quantities of plasma were used and little precaution was observed in the exclusion of donors with previous histories of jaundice. The use of these large amounts of dried and frozen plasma may have contributed to the high incidence of hepatitis. As McGraw [15] pointed out, drying and freezing are excellent methods for preserving virus. Moreover, repeated passage of the virus through many persons undoubtedly enhanced its virulence. It should be noted that many of the cases reported in children occurred during the years 1942 to 1945, when the general incidence was highest.

During these years, the plasma which we employed for intramuscular injection was obtained only from our own blood bank from small groups of selected donors; consequently, smaller pools were prepared, and this fact naturally excluded to a great extent contaminated plasma.

4. *Physical Status.*—A review of the cases of homologous serum hepatitis in adults and children emphasizes the frequent association of the disease with impaired nutrition and preexisting systemic disease, particularly liver damage. These conditions may represent the "unknown secondary factors" which were referred to by the investigators of the British Ministry of Health [19] when they studied large numbers of cases of hepatitis. They believed that the disease was not due to the presence of the virus alone but that it was essential to have a previously damaged liver or a state of generally lowered resistance. Fox [6] suggested that a secondary etiological factor must be present in addition to the primary agent in the blood, and this factor could be chronic intoxication of the liver or lowered hepatic resistance due to dietary deficiency. In his report on hepatitis following inoculation with yellow fever vaccine in Brazil, he noted that a great part of the population suffered from malnutrition. Cameron [20] observed that his patients were seriously debilitated, and Findlay and MacCallum [5] reported similar findings.

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17. Propert.[2] MacNalty.[8] Iablokova, M. L.: Modes of Dissemination of Infectious Hepatitis, Soviet Med. **4**:7, 1949.

18. Thalhimer, W.: Intravenous Injection of Pooled Normal Plasma or Serum: Is It Dangerous? J. A. M. A. **120**:1263 (Dec. 19) 1942.

19. Homologous Serum Jaundice, Memorandum Prepared by Medical Officers of the Ministry of Health, Lancet **1**:83 (Jan. 16) 1943.

20. Cameron, J. D. S.: Infective Hepatitis, Quart. J. Med. **12**:139 (July) 1943.

In children, impaired nutrition and/or gastrointestinal intoxication were noted in the cases reported by Apley and Wallis [21] (two cases), Schmidt and Lee,[22] Moloshok [23] (cases 2, 3, 5, 6 and 8), Scheinberg [24] (one case) and Rosenblum [25] (one case).

Three of the patients whose cases were reported by Bruyn,[26] Wood and Black [27] and Moloshok [23] (case 4) had been treated for hemolytic anemia of the newborn and icterus gravis. Liver damage is known to be an integral part of this condition,[28] and Rosenblatt [29] reported three cases of massive necrosis of the liver in infants with erythroblastosis fetalis after exchange transfusions.

It is apparent, therefore, that a considerable amount of liver damage had already existed in all these children before the development of hepatitis. Unless liver function is impaired, there is less likelihood of producing this disease. To account for the complete lack of occurrence of the disease in our series of cases, despite the fact that some of our children were malnourished or had some systemic disease, it must be assumed either that liver damage was minimal or that there was an absence of virus because of the careful collection of plasma.

Hepatitis Without Jaundice.—Many cases of infectious hepatitis have been reported in which there was no manifest jaundice. Barker, Capps and Allen [30] described such instances in the Mediterranean Theater during World War II. Webb [31] reported a series of 43 cases of hepatitis in children, in 21 of which icterus developed and in 22 of which it did not. Clinical manifestations and results of laboratory tests were identical in both icteric and nonicteric groups. Although every reported case of homologous serum hepatitis in children was associated with manifest jaundice, the possibility of nonicteric hepatitis could not be overlooked in our study. None of the 22 children investigated 50 to 100 days after an injection of plasma revealed any evidence of hepatic dysfunction. It was interesting to note that while this study was being conducted four patients with infectious mononucleosis revealed some disturbance of liver function without jaundice.

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21 Apley, J., and Wallis, H. R. E.: Homologous Serum Jaundice in Infancy, Brit. M. J. **1**:197 (Jan. 31) 1948.

22. Schmidt, E. C. H., and Lee, C. H.: Fatal Homologous Serum Hepatitis in a Young Infant, J. Pediat. **34**:266 (Feb.) 1949.

23. Moloshok, R. E.; Karelitz, S., and Strauss, L.: Homologous Serum Hepatitis in Infants and Children, Pediatrics **3**:651 (May) 1949.

24. Scheinberg, I. H.; Kinney, T. D., and Janeway, C. A.: Homologous Serum Jaundice, J. A. M. A. **134**:841 (July 5) 1947.

25. Rosenblum, A. H.; Lander, H., and Popper, H.: Lipoid Nephrosis Complicated by Homologous Serum Jaundice, J. Pediat. **35**:465 (Oct.) 1949.

26. Bruyn, H. B.: Homologous Serum Hepatitis Following Transfusion in an Infant, J. Pediat. **31**:60 (July) 1947.

27. Wood, D. A., and Black, M. B.: Further Notes on the Pathology of Acute Epidemic Hepatitis and Homologous Serum Jaundice, Am. J. Clin. Path. **16**:746 (Dec.) 1946.

28. Wallerstein, H.: Personal communication to the authors.

29. Rosenblatt, P.: Massive Necrosis of Liver Following Exchange Transfusion for Erythroblastosis Fetalis, Am. J. Clin. Path. **18**:700 (Sept.) 1948.

30. Barker, M. H.; Capps, R. B., and Allen, F. W.: Acute Infectious Hepatitis in the Mediterranean Theatre Including Acute Hepatitis Without Jaundice, J. A. M. A. **128**:997 (Aug. 4) 1945.

31. Webb, C. H.; Wolfe, S. G.; Lucas, R. T., and Anderson, C. E.: Acute Hepatitis in Children: Clinical Features and Laboratory Tests, South. M. J. **40**:340 (April) 1947.

Gamma Globulin.—Of all forms of prophylaxis to employ, use of gamma globulin would seem to be the safest and most convenient. Unfortunately, the source of supply tended to be variable, and at the time of greatest need it was not always available. During the measles epidemic year of 1947-1948, the supply was so inconstant that it was necessary to use mostly pooled plasma. It has also been observed that the protective effect of gamma globulin has not been quite so good as that obtained with pooled plasma.

SUMMARY

A study was made of the incidence of homologous serum hepatitis in a series of 13,755 children between the ages of 3 months and 12 years who received intramuscular injections of human plasma, serum and gamma globulin for prophylaxis against ward contagion. Of these children, 11,447 were studied at the Morrisania City Hospital over a 15 year period and 2,308 at the Jewish Memorial Hospital for five years.

A comparison was made with 27,598 children admitted to two other city hospitals which did not employ routine prophylactic injections.

Among the 13,755 children under our care, 35 children with jaundice were admitted to our hospital and 85 to the other hospitals.

Of the 35 children in our hospital, 25 had not received previous injections, and 10 had been given prophylactic injections.

In the 10 children who had received injections jaundice developed more than one year after inoculation.

In none of the children did jaundice develop less than one year after inoculation.

Twenty-two children studied for hepatitis without jaundice were found to have no evidence of liver dysfunction, as indicated by results of the various tests.

The factors which predispose children to the development of homologous serum hepatitis have been discussed.

The Director of Pediatrics at Lincoln Hospital, Dr. Harry Altman, and the Director of Pediatrics at Fordham Hospital, Dr. Joseph Golomb, cooperated in this study.

TETANUS IMMUNIZATION

A Ten Year Study

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THE IMMUNIZATION against tetanus with tetanus toxoid alone or combined with diphtheria toxoid and at times with added pertussis vaccine has now become an accepted practice in preventive medicine. There have been many reports on the immediate effectiveness of this procedure but few on longer term immunity levels. Peshkin [1] gave booster injections of tetanus toxoid to 25 children four years after basic immunization, and the titers rose to at least 0.1 unit in each child. Fifteen children were given tetanus booster injections by McBryde and Poston,[2] and their antitoxin levels became 0.1 to 12.0 units one week later. Miller, Ryan and Beard,[3] using fluid and alum-precipitated toxoid, gave booster injections to 20 children four to seven years after basic immunization, and their antitoxin levels rose to at least 0.1 unit within seven days. Long and Sartwell [4] and Baird [5] gave booster injections to seven and 23 adults respectively three to five years after basic immunization and received an adequate response. Six of Baird's patients had had previous booster injections.

Opinion differs as to what the protective level of tetanus antitoxin in the blood serum should be to offer immunity against the disease. The figures most commonly expressed are 0.01 to 0.1 unit of antitoxin per cubic centimeter of blood serum.

METHOD AND OBSERVATIONS

The material for this report is from a group of 300 infants and children, most of whom were immunized between 1938 and 1940. During the intervening years 262 of these children

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From the Children's Memorial Hospital and the Ortho S. A. Sprague Memorial Institute Laboratories.

The tetanus toxoid used in this study was supplied by Eli Lilly & Company, Indianapolis. Mr. F. G. Jones, Head of the Immunizing Biological Research Department of Eli Lilly & Company, checked titrations on some of the children studied.

1. Peshkin, M. M.: Immunity to Tetanus Induced by a Third Dose of Toxoid Four Years After Basic Immunization, Am. J. Dis. Child. **69**:83 (Feb.) 1945.

2. McBryde, A., and Poston, M. A.: Immunization with Tetanus Toxoid, J. Pediat. **28**:692 (June) 1946.

3. Miller, J. J., Jr.; Ryan, M. L., and Beard, R. R.: The Speed of the Secondary Immune Response to Tetanus Toxoid with a Review of the War Reports and Observations on the Simultaneous Injection of Toxoid and Antitoxin, Pediatrics **3**:64 (Jan.) 1949.

4. Long, A. P., and Sartwell, P. E.: Tetanus in United States Army in World War II, Bull. U. S. Army M. Dept. **7**:371 (April) 1947.

5. Baird, H. W.: The Duration of Immunity to Tetanus, Yale J. Biol. & Med. **21**:385 (May) 1949.

have had 1,363 titrations of their blood serum for tetanus antitoxin. A preliminary report [6] on the immediate results of their immunization was made in 1941.

The ages at the time of the primary inoculations were from 6 months to 1 year in 74 cases, 1 to 2 years in 62 cases, 2 to 3 years in 36 cases, 3 to 5 years in 38 cases and 5 to 12 years in 52 cases. Tetanus toxoid, alum-precipitated, and combined tetanus and diphtheria toxoid, plain or alum-precipitated, were used in doses of 0.5 or 1 cc. Some children received two and others three injections for their basic immunization. Many have received one or more booster injections during the intervening 10 years.

The children studied have been divided into the following groups: (1) those receiving two injections for basic immunization, (2) those receiving three injections for basic immunization, (3) those of group 1 receiving booster injections, (4) those of group 2 receiving booster injections, (5) those of both groups receiving multiple booster injections.

Two Injection Group.—In table 1 are given the titrations on 185 children receiving two injections for primary immunization. Also included are the titrations between the second and third injections of 77 children receiving three injections for their basic immunization. These would be the same for the two groups.

TABLE 1.—*Blood Serum Titrations for Tetanus Antitoxin After Two Injections of Tetanus Toxoid for Basic Immunization*

Antitoxin Levels, Units	Intervals After Basic Immunization													No. of Titrations
	1-2 Wk.	2-4 Wk.	1-3 Mo.	3-6 Mo.	6-12 Mo.	1-2 Yr.	2-3 Yr.	3-4 Yr.	4-5 Yr.	5-6 Yr.	6-7 Yr.	7-8 Yr.	8-9 Yr.	9-10 Yr.	
0.003 to 0.01	7	..	1	4	..	3	4	2	..	..	..	1	..	..	22
0.01 to 0.1	6	..	2	4	22	42	29	23	11	15	7	3	2	1	167
0.1 to 0.2	11	2	5	9	27	22	15	8	5	3	..	..	..	..	107
0.2 to 0.5	5	3	13	14	21	26	7	5	2	2	1	1	1	1	102
0.5 to 1.0	10	5	16	22	13	7	3	..	..	..	..	..	..	..	76
1.0 to 2.0	4	8	17	10	1	1	1	..	..	..	..	..	..	..	42
2.0 to 5.0	7	20	19	2	1	1	..	..	..	..	..	..	..	..	50
5.0	3	6	10	1	..	..	..	..	..	..	..	..	..	..	20
10 to 15	5	7	..	..	..	..	..	..	..	..	..	..	..	..	12
15 to 35	4	1	..	..	..	..	..	..	..	..	..	..	..	..	5

Eight children had low blood serum titers of tetanus antitoxin of more than 0.003 unit but less than 0.01 unit up to three months after the second injection. Three of these eight children had no change in their titers for two years, at the end of which time they were given booster injections. There was an immediate rise in titer of 0.2 to 5.0 units, these later receding to 0.01 for the next several years. Two of these three children were given second booster injections four to eight years later, and their levels immediately rose to 2.0 to 10.0 units. The remaining five children had some increase in their antitoxin levels after the first week, to at least 0.01 unit level, at which two remained for from six to seven years. The other three received booster injections one to two years later with an immediate increase of from 0.5 to 2.0 units.

Of the four children with 0.003 unit levels at three months, three received their third injections with an immediate high response and one did not return for further study. Of the other children having decreases in titers to 0.003 unit one to eight years later, three received booster injections, with an immediate satisfactory response of from 0.5 to 2.0 units. Children with early 0.01 to 0.1 unit levels followed the same pattern as those with 0.003 unit levels.

6. Bigler, J. A., and Werner, M.: Active Immunization Against Tetanus and Diphtheria in Infants and Children, J. A. M. A. **116**:2355 (May 24) 1941.

Satisfactory levels were obtained in most of the children within the first six months, but after that time there was a decrease of all levels with the largest number in the 0.01 to 0.1 unit groups.

Three Injection Group.—Three injections were used for basic immunization in 77 children. The blood serum titrations for this group are given in table 2. The greatest difference between the two and three injection groups is the absence of low

TABLE 2.—*Blood Serum Titrations for Tetanus Antitoxin After Three Injections of Tetanus Toxoid for Basic Immunization*

Antitoxin Levels, Units	Intervals After Basic Immunization													No. of Titrations
	1-2 Wk.	2-4 Wk.	1-3 Mo.	3-6 Mo.	6-12 Mo.	1-2 Yr.	2-3 Yr.	3-4 Yr.	4-5 Yr.	5-6 Yr.	6-7 Yr.	7-8 Yr.	8-9 Yr.	9-10 Yr.	
0.003 to 0.01	..	..	..	..	1	2	..	1	1	..	..	1	..	..	6
0.01 to 0.1	..	..	..	..	1	7	9	9	10	12	5	5	4	4	66
0.1 to 0.2	..	..	..	1	9	14	9	11	7	3	1	..	..	..	55
0.2 to 0.5	2	..	..	3	9	14	14	3	1	3	1	2	1	..	53
0.5 to 1.0	5	..	1	..	9	7	5	..	..	1	..	..	..	..	28
1.0 to 2.0	10	2	3	1	5	3	2	..	..	..	..	..	..	..	26
2.0 to 5.0	13	7	1	..	2	..	..	..	..	..	..	..	..	..	23
5.0	9	4	1	..	..	..	..	..	..	..	..	..	..	..	14
10 to 15	3	2	..	..	..	..	..	..	..	..	..	..	..	..	5
15 to 35	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..

TABLE 3.—*Blood Serum Titrations of Tetanus Antitoxin Following a Booster Injection After Two Injection Basic Immunization*

Antitoxin Levels, Units	Number of Children and Intervals Between Basic Immunization and Booster Injection														
	Levels Before Booster Injection	Intervals After Booster Injection													No. of Titrations
		1-2 Wk.	2-4 Wk.	1-3 Mo.	3-6 Mo.	6-12 Mo.	1-2 Yr.	2-3 Yr.	3-4 Yr.	4-5 Yr.	5-6 Yr.	6-7 Yr.	7-8 Yr.	8-9 Yr.	9-10 Yr.	
	..	..	..	..	..	23	29	33	10	3	4	..	2	1	1	
0.003 to 0.01	5	..	..	..	..	..	..	..	1	..	..	1	..	1	1	4
0.01 to 0.1	44	..	..	..	..	1	6	12	9	15	9	5	5	2	..	64
0.1 to 0.2	23	..	..	..	2	1	13	11	9	4	1	1	..	..	..	42
0.2 to 0.5	23	1	..	..	1	4	18	21	5	3	2	1	1	..	..	57
0.5 to 1.0	8	3	2	..	1	6	14	7	2	1	1	..	1	..	..	38
1.0 to 2.0	..	13	1	1	..	2	3	3	..	..	..	1	..	..	..	24
2.0 to 5.0	1	24	5	1	1	..	5	..	..	..	..	..	..	..	..	36
5 to 10	..	16	6	1	1	..	1	..	..	..	..	..	..	..	..	25
10 to 15	..	9	3	1	..	..	..	..	..	..	..	..	..	..	..	13
15 to 35	..	3	1	..	..	..	..	..	..	..	..	..	..	..	..	4

titrations under six months in the latter. The third injection really acts like a booster injection. After the six month period there is relatively little difference in the level of titrations of the two groups. Many children in both groups have a decrease in the level of titrations to 0.01 unit after the sixth month. It would seem that either two injections or three injections give adequate basic immunity.

Booster Injections After Two Injection Immunization.—Booster injections were given to 106 children in this group (table 3). The upper line gives the number of children and the interval between their basic immunization and the booster injections. In the first column are given the levels of antitoxin before the booster injections. Nearly 75 per cent of the children fall into the 0.1 to 0.003 unit level group.

All children responded with adequate titers after booster injections given from six months to 10 years after basic immunization. The level of titers was similar to that seen after the third injection in the group receiving three inoculations for basic immunization. Those children with low titers before the booster injections responded as well as those with higher titers, and the length of the interval before the booster injections did not influence the levels attained.

Again, as in the previous group, after the sixth month to one year interval there was a rather rapid decrease in the titers to the lower levels.

TABLE 4.—*Blood Serum Titrations of Tetanus Antitoxin Following a Booster Injection After Three Injection Basic Immunization*

	Number of Children and Intervals Between Basic Immunization and Booster Injection														
	Levels Before Booster	..	..	..	..	..	3	15	4	..	2	..	3	3	2	
		Intervals After Booster Injection														
Antitoxin Levels, Units	Injection	1-2 Wk.	2-4 Wk.	1-3 Mo.	3-6 Mo.	6-12 Mo.	1-2 Yr.	2-3 Yr.	3-4 Yr.	4-5 Yr.	5-6 Yr.	6-7 Yr.	7-8 Yr.	8-9 Yr.	9-10 Yr.	No. of Titrations
0.003 to 0.01	2	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
0.01 to 0.1	10	..	..	..	..	..	9	3	1	2	1	2	..	..	..	11
0.1 to 0.2	9	..	..	..	..	..	3	2	1	1	1	1	..	..	..	9
0.2 to 0.5	8	..	..	1	..	1	4	4	6	3	..	1	1	..	..	21
0.5 to 1.0	1	1	..	..	..	1	4	1	3	..	..	..	..	..	..	10
1.0 to 2.0	1	1	..	..	..	..	5	2	..	1	..	..	..	..	..	9
2.0 to 5.0	..	3	4	1	..	..	2	..	..	..	..	..	..	..	..	10
5 to 10	..	3	1	2	..	..	..	..	..	..	..	..	..	..	..	6
10 to 15	..	2	6	2	..	..	1	..	..	..	..	..	..	..	..	11
15 to 35	..	2	4	..	..	..	..	..	..	..	..	..	..	..	..	6

TABLE 5.—*Blood Serum Titrations of Tetanus Antitoxin Following Multiple Booster Injections*

	Intervals After Booster Injection												
Antitoxin Levels, Units	1-2 Wk.	2-4 Wk.	1-3 Mo.	3-6 Mo.	6-12 Mo.	1-2 Yr.	2-3 Yr.	3-4 Yr.	4-5 Yr.	5-6 Yr.	6-7 Yr.	7-8 Yr.	No. of Titrations
0.01 to 0.1	..	..	..	..	..	..	2	2	4	1	..	..	9
0.1 to 0.2	..	..	..	..	..	..	8	3	2	..	..	..	8
0.2 to 0.5	..	..	..	..	..	2	6	6	..	..	1	1	16
0.5 to 1.0	1	..	..	1	..	5	..	..	2	..	..	..	9
1.0 to 2.0	7	2	..	..	1	1	..	1	..	..	..	..	12
2.0 to 5.0	5	1	2	..	2	2	2	..	..	..	..	..	14
5 to 10	1	1	..	..	..	2	..	..	..	..	..	..	4
10 to 15	4	4	..	..	..	..	..	..	..	..	..	..	8
15 to 35	..	4	..	..	..	..	..	..	..	..	..	..	4

Booster Injections After Three Injection Immunization.—The upper line in table 4 gives the number of children and the interval between the primary immunization and the booster injections. In column 1 are the titration levels at the time of the booster injections. There was an immediate good response in all cases, and the levels tended to remain moderately higher than in group 3 but many decreased to the 0.01 unit level after the first year. Unfortunately, too few titrations were done during the third to twelfth month period.

Multiple Booster Injections.—Thirty-nine children received two or more booster injections after their primary immunization of two or three injections. Two booster injections were given to 30 children, three to five children and four to four children (table 5). These were given from two to 10 years after the primary

immunization. One child, 8 years of age, had a titer of 0.01 unit one week after his second booster injection. There must have been a high rise in titer, because at the end of one year the level was still 0.5 unit and 0.2 unit at the second and third year intervals. This boy had a good response after his first booster injection one year after his two injection immunization.

There was an equally good response to each of the multiple booster injections. There was no evidence of depression of antitoxin formation with multiple stimulations. Titers tended to remain higher for longer periods than after single booster injections.

Interval Between Injections for Basic Immunization.—The intervals between the injections for basic immunization varied considerably. In 54 cases the interval was one month; in 17 cases, two months; in 145 cases, three months, and in 12 cases, four to six months.

In addition, 28 children had their second injections from six to 12 months after the first, and six children had injections at an interval varying from 12 to 51 months. One to four weeks after the second injections administered to this group, the titers ranged from 0.5 to 35 units with eight titers of from 10 to 35 units. Three to six months later the lowest titer was 0.2 unit. After six months the titers ranged in the same levels as were present in the other children. Nineteen of these 34 children received one or more booster injections one to seven years later, with the same excellent response. This group with the long interval between the injections for basic immunization had higher average titers than did the group with shorter intervals. It would seem that one need not be concerned when a long interval occurs between injections.

COMMENT

Adequate basic immunization can be obtained from either two or three injections of tetanus toxoid. In the three injection group the third injection acted like a booster injection. The stimulation of a booster injection was adequate up to nine years after primary immunization and would undoubtedly be just as effective for many more years. An adequate response was obtainable from as many as five booster injections in the same child.

There was no difference in the response to the booster injection in relation to the interval between the basic immunization and the booster injection. Peshkin [1] found the response better after four years than when the interval was shorter. Miller, Ryan and Beard [3] reported that when the interval was greater than four years the speed of response was occasionally lessened.

From this study it would seem that the more injections given, the longer the antitoxin titers remain above 0.1 to 0.2 unit. After the two injection immunization, many titers decrease below this level after one month; after three injections, such levels are reached only after three to six months; and after four injections, only after six to 12 months.

Rapidity of Booster Response.—The titers reported in the tables were taken one week or more after the booster injections. To ascertain how rapid was the response

to a booster injection, titrations were done daily on three children after such an injection with the following results:

Date	Immunization	Tetanus Antitoxin Titers per Cc. of Blood Serum	
Case 1 (born April 8, 1938)			
4/ 7/39	1 cc. combined diphtheria and tetanus alum-precipitated toxoid	.....	
7/ 7/39	1 cc. combined diphtheria and tetanus alum-precipitated toxoid	+0.006	—0.01
8/ 4/39		+2.0	—5.0
11/13/44		+0.01	—0.1
11/20/45		+0.01	—0.1
11/21/46		+0.01	—0.1
6/ 6/47	0.5 cc. alum-precipitated tetanus toxoid (booster)	0.017	.....
6/ 7/47		0.017	.....
6/ 8/47		0.017	.....
6/ 9/47		0.05	.....
6/10/47		0.05	.....
6/11/47		0.1	.....
6/12/47		0.5	.....
6/13/47		1.0	.....
6/19/47		4.0	.....
Case 2 (born Aug. 27, 1935)			
6/26/42	0.5 cc. alum-precipitated tetanus toxoid	.....	
9/25/42	1 cc. combined diphtheria and tetanus alum-precipitated toxoid	.....	
10/24/42		+0.2	—0.5
1/14/44		+0.01	—0.1
10/ 7/44		+0.01	—0.1
10/13/45		+0.01	—0.1
10/ 4/46		+0.01	—0.1
6/27/47	0.5 cc. alum-precipitated tetanus toxoid (booster)	0.01	.....
6/29/47		0.01	.....
6/30/47		0.01	.....
7/ 1/47		0.017	.....
7/ 2/47		0.05	.....
7/ 9/47		1.0	.....
Case 3 (born Sept. 29, 1937)			
6/ 8/41	1,500 units tetanus antitoxin	.....	
9/ 3/46	1,500 units tetanus antitoxin	.....	
11/ 4/46	0.5 cc. alum-precipitated tetanus toxoid	.....	
12/13/46	1 cc. alum-precipitated tetanus toxoid	.....	
6/12/47	1 cc. alum-precipitated tetanus toxoid (booster)	.....	
6/14/47		0.05	.....
6/15/47		0.1	.....
6/16/47		0.2	.....
6/17/47		0.5	.....

Alum-precipitated toxoid was used for the booster injections, and it was given six months to eight years after primary immunization. The increase of antitoxin began on the third or fourth day, after which the rise was rapid. These results compare with those of Boyd,[7] who reported that the increase occurs about the fifth day. Miller, Ryan and Beard [8] reported that fluid toxoid used for reinjection induced a more rapid rise in antitoxin than alum-precipitated toxoid. They feel that antitoxin and toxoid should be given simultaneously when immunization occurred more than four years previously. The response I obtained with alum-precipitated toxoid was equally as rapid as that reported with fluid toxoid, and there was no decrease in the response after a four year interval. Because of this we do not use tetanus antitoxin with the booster injections of toxoid. Titers of antitoxin can be

7. Boyd, J. S. K.: Tetanus in African and European Theatres of War 1939-1945, Lancet **1**:113 (Jan. 26) 1946.

increased rapidly even in those children who had their primary injections up to 10 years previously. The rapidity of this response is important because signs of tetanus usually appear from seven to 14 days after an injury.

CONCLUSIONS

1. A primary or basic immunization can be obtained with either two or three injections of tetanus toxoid.

2. When two injections are used for basic immunization, protective levels are not always attained and a booster injection should always be given after an injury, no matter how short the interval.

3. Detectable amounts of tetanus antitoxin were present in the blood serum of all immunized children tested up to 10 years later during the study.

4. All children had protective levels of antitoxin after booster injections given up to 10 years after immunization.

5. Protective levels were obtained with each of as many as five booster injections.

6. The response to the booster injections was rapid, occurring within the first seven days.

7. The greater the number of injections, the longer protective levels were maintained.

8. Until there are further reports on antitoxin levels over long intervals, although apparently protective levels are present, it would seem advisable to give a booster injection to an immunized person at the time of an injury from which tetanus might develop.

MENTAL ACHIEVEMENT OF CONGENITALLY HYPOTHYROID CHILDREN

A Follow-Up Study of Twenty Cases

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CONGENITAL hypothyroidism is a disease for which specific therapy is available. It would seem, then, that if treatment were instituted early, and continued adequately and uninterruptedly, satisfactory results ought to be forthcoming. As far as physical results are concerned, reports in the literature are uniformly enthusiastic. In regard to mental results, however, reports are conflicting.

Some investigators believe that good mental results in cretins depend on early and adequate treatment.[1] Other authors are not so optimistic. As early as 1910, Siegert [2] reported severe mental retardation in some cretins despite prolonged and satisfactory treatment. In 1927 Lucas [3] said that "normal mentality is almost never attained." Tredgold [4] similarly reported on a number of cretins who showed no mental improvement with treatment. Kimball and Marinus,[5] after an extensive study of the subject, concluded that "cretins are predestined at a fixed low mental age. If untreated, they seldom go beyond 6 years; if treated, they go approximately to 8 years." Holt [6] wrote that he had not seen normal mental development in a cretin, even when treatment was begun during the first year. Aldrich [7] also stressed the frequent mental retardation in apparently well treated cretins. Gesell, Amatruda and Culotta [8] also believe that mental progress is not entirely contingent on therapy. Lewis [9] thought that in the majority of cretins there is only a rough

From the Pediatric Service of Dr. Horace L. Hodes, Mount Sinai Hospital.

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2. Siegert, F.: Ergebn. d. inn. Med. u. Kinderh. **6**:601, 1910.

3. Lucas, W. P.: The Modern Practice of Pediatrics, New York, The Macmillan Company, 1927.

4. Tredgold, A. F.: Mental Deficiency, ed. 5, New York, William Wood & Company, 1929.

5. Kimball, O. P., and Marinus, C. J.: Ann. Int. Med. **4**:569, 1930.

6. Holt, L. E., and Howland, J.: Holt's Diseases of Infancy and Childhood: A Textbook for the Use of Students and Practitioners, revised by L. E. Holt Jr. and R. McIntosh, New York, D. Appleton-Century Company, Inc., 1936.

7. Aldrich, C. A.: J. Pediat. **8**:381, 1936.

8. Gesell, A.; Amatruda, C. S., and Culotta, C. S.: Effect of Thyroid Therapy on Mental and Physical Growth of Cretinous Infants, Am. J. Dis. Child. **52**:1117 (Nov.) 1936.

9. Lewis, A.: Lancet **1**:1505; **2**:5, 1937.

correlation between treatment and the intellectual level attained. Goodkind and Higgins,[10] after studying a group of cretins that they had followed for 5½ to 24 years, concluded that adequacy of treatment was by no means the deciding factor in the ultimate mental level. Wagner[11] still more pessimistically wrote that "progressive stages of deterioration are never completely reparable."

Bruch and McCune,[12] in reporting on a group of 23 cretins, described only three with normal intelligence. The mean intelligence quotient for this group was 62, and this figure did not seem to be affected by the age at which treatment was begun. Most recently, Radwin and his co-workers,[13] who had followed a group of cretins into adult life, observed that in 25 per cent of this group no positive relationship could be demonstrated between treatment and ultimate mental achievement.

The consensus seems to be that there is a discrepancy between therapy and ultimate mental attainment.

Some of the factors implicated in this discrepancy have been (1) the "maturity status" before treatment (Bruch and McCune[12]); (2) an inherent capacity for learning (Gesell[8]); (3) environmental factors, such as special educational aids and intelligent family cooperation,[14] and (4) a concomitant defect of cerebral development. Of these, the first three undoubtedly play an important role; the second and third are significant in euthyroid, as well as hypothyroid, states; however, cerebral impairment, existing either as a primary amentia or as a result of prenatal (or postnatal) lack of thyroid, seems to be the most significant factor involved in unsatisfactory mental progress of cretins.

Such a hypothesis was first advanced by Tredgold,[4] who postulated two types of cretins; in the first type symptoms are clearly due to hypothyroidism, and the child can become normal with treatment; symptoms in the other type are due to a primary amentia in association with hypothyroidism, in which case the child cannot become normal.

That cerebral defect should be associated with thyroid defect is easily understood. The tendency for congenital defects to be multiple rather than single is well known. The same etiological factor that is responsible for the thyroid defect may also account for the cerebral defect. Further, that cerebral defect should result from thyroid defect is also easily understood.

In animals thyroidectomy produces a distortion of differential development which affects the central nervous system, as well as all other tissues of the body.

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10. Goodkind, R. P., and Higgins, H. L.: New England J. Med. **224**:722, 1941.

11. Wagner, R.: Endocrine Problems in Childhood, read before the annual meeting of the Massachusetts Medical Society, Boston, May 26, 1943.

12. Bruch, H., and McCune, D. J.: Mental Development of Congenitally Hypothyroid Children: Its Relationship to Physical Development and Adequacy of Treatment, Am. J. Dis. Child. **67**:205 (March) 1944.

13. Radwin, L. S.; Michelson, J. P.; Kramer, B., and Berman, A. B.: End Results in Treatment of Congenital Hypothyroidism: Follow-Up Study of Physical, Mental and Behavioral Developments, Am. J. Dis. Child. **78**:821 (Dec.) 1949.

14. McDonald, J. W.; Brown, A. W., and Bronstein, I. P.: Background and Social Adjustment of Thyroid-Deficient Children Receiving Glandular Therapy, Am. J. Dis. Child. **59**:1227 (June) 1940.

Isenschmid,[15] in experiments with cats, showed that thyroidectomy was followed by changes in practically all cells of the central nervous system.

In the human embryo the thyroid gland develops early. According to Norris,[16] follicles are already present at the 24 mm. stage and colloid is seen at the 60 mm. stage. The fetal gland has been shown to take up radioiodine as early as the fourteenth week. The function of the gland is to increase irritability of all living tissue, and, as Means [17] has said, "the nervous system, being the tissue which is most capable of displaying irritability, exhibits the most pronounced effect."

Already in the sixteenth century, Paracelsus recognized that in hypothyroidism there may be a lack of development of cortical areas of the brain, and in the succeeding 400 years no one has challenged this statement. It seems remarkable, therefore, that the otherwise voluminous literature on this subject should display such a dearth of reports on investigation of the cortical areas of cretins.

In 1885 Hadden [18] reported cortical atrophy in the brains of two cretins who came to autopsy. In 1910 Siegert [2] summarized the early literature by stating that the brains of cretins show developmental disturbance such as is observed in other forms of idiocy. Following this, Lotmar [19] reported observing histological changes in the brain cells of cretins on autopsy and concluded that when thyroid deficiency occurs early it causes disturbances in the development of the brain.

Direct investigation of the intact brains of living subjects was made possible some 15 years ago with the discovery of methods of electrophysiology, yet such studies on cretins are remarkably few. Kreezer [20] in 1937 studied the electroencephalographic patterns of a few cretins and reported "a relative low frequency of alpha waves." He related this to a reduced rate of oxidation of cortical cells caused by thyroid deficiency.

Bruch and McCune [12] reported the result of pneumoencephalography in a cretin in whom mental development had not kept pace with somatic growth. They found "considerable difference in the size of the lateral ventricles with dilatation of the left ventricle." In this child postnatal anoxia and jaundice "probably added further damage to a congenitally imperfect brain."

Aside from these meager reports, direct investigations of the brains of mentally retarded cretins are conspicuous by their absence from the literature.

MATERIAL AND METHOD

In an attempt to explain the mental retardation of several cretins who had presumably received adequate thyroid therapy over long periods, electroencephalographic studies were made on 13 such persons. These 13 are part of a larger group of cretins who have been under my observation. The results are interesting, perhaps significant, and constitute a reason for adding still another paper to the already ample literature on hypothyroidism in childhood.

15. Isenschmid, R.: Frankfurt. Ztschr. f. Path. **21**:321, 1918.

16. Norris, E. H.: Am. J. Anat. **20**:411, 1916.

17. Means, J. H.: The Thyroid and Its Diseases; From the Thyroid Clinic of the Massachusetts General Hospital, ed. 2, Philadelphia, J. B. Lippincott Company, 1948, p. 44.

18. Hadden, W. B.: Lancet **1**:709, 1885.

19. Lotmar, F.: Ztschr. f. d. ges. Neurol. u. Psychiat. **119**:491, 1929.

20. Kreezer, G.: Proc. Am. A. Ment. Deficiency **42**:130, 1937.

21. Footnote deleted.

The purpose of this paper, then, is twofold: (1) to present the results of a review of data on 20 cretins who have been followed for one to 25 years and (2) to report on the electroencephalographic findings in 13 of this group.

In this group there were six boys and 14 girls. One of the children (case 17) is believed to have juvenile hypothyroidism, acquired at the age of about 4 years. All the others have congenital hypothyroidism, or what will be termed conveniently (if somewhat erroneously) "cretinism."

The cases are briefly summarized. Since the clinical picture of cretinism has been so frequently and so adequately described in the literature, no mention will be made of physical findings. When a diagnosis was made for an untreated cretin, it was based on the usual clinical, roentgenologic and laboratory findings and response to therapy. When a treated cretin was seen by me, the diagnosis having previously been made elsewhere, therapy was interrupted for a time only to confirm the diagnosis.

Psychometric tests were performed, for the most part, in the Child Guidance Clinic. The usual battery of tests was applied in practically every case. This included the Terman-Merrill Revised Stanford-Binet Intelligence Scale, Forms L and M, the Pintner-Paterson scale, the Wechsler-Bellevue Intelligence Scale for Adults and Adolescents, the Porteus Maze test, the Kohs block test, the Goodenough test, the Bender visual-motor Gestalt test, the Rorschach test and, in infants, the Gesell developmental scales. Unless striking discrepancies occurred, the separate results of these tests are not mentioned in the individual case reports.

Desiccated thyroid U. S. P. was used for all patients. The individual dosage is not mentioned in the reports, since it varied from case to case and from time to time. Individual clinical response has always been the best guide to adequate dosage. In several cases, when the dose was increased in an effort to stimulate bone maturation or to influence the cholesterol level or the mental progress, I noted, not increased progress, but increased irritability and personality disturbances. I have learned that the most satisfactory dose of thyroid is that which is required by the individual cretin for his physical progress. This observation was originally recorded in the literature by Bruch and McCune.[12]

REPORT OF CASES

CASE 1.—A. R., a white female infant, was admitted to the hospital at the age of 15 months. The mother was diabetic; the father had been thyroidectomized several years prior to the infant's birth. A diagnosis of cretinism was made on the basis of the clinical picture and the retardation of carpal development. Total blood lipids were 2,500 mg. and cholesterol was 285 mg. per 100 cc. Psychometric tests made before therapy was instituted showed a developmental quotient of 60.

The infant made a rapid response to thyroid therapy. The cholesterol dropped to 200 mg. and blood lipids to 1,270 mg. per 100 cc. The child was discharged from the hospital, to be followed in the Growth and Development Clinic.

After 1½ years of therapy, the bone age appeared to be within normal limits, and the child seemed physically normal. Her intelligence quotient at this time was 77, a gain of 17 points. In the light of Gesell's recent observations, if this initial response to therapy had been an index of the child's ultimate mental capacity, she should have made mental progress. This was not the case, however. At the age of 7 years the intelligence quotient was only 61; at the age of 11 years it was 50. The child is now 12 years old. Her physical development and bone and sexual maturation have proceeded normally. Mentally, however, she functions on a defective level in spite of adequate treatment since the age of 15 months.

The question can, of course, be raised whether the mental results might have been better had treatment been started earlier in infancy. However, other children in this group whose treatment was begun even later attained normal mental levels; electroencephalographic studies in this patient revealed "diffuse cerebral dysfunction" (fig. 1).

In this case, cerebral impairment explains the discrepancy between adequate therapy and mental achievement. Where such impairment exists, mental progress cannot keep pace with physical progress, no matter how adequate the treatment.

CASE 2.—J. B., a white female child, was first admitted to the hospital at the age of 2 years. Physical examination showed obvious hypothyroidism. The fontanel was wide open; the bone age was estimated at 5 months. Cholesterol was 300 mg. per 100 cc.; alkaline phosphatase

was 7 King-Armstrong units. The family history may have been significant in that the parents both came from a goitrous section of Germany.

When thyroid was administered, the child responded quickly. The cholesterol fell to 220 mg. per 100 cc.; alkaline phosphatase rose to 16.5 King-Armstrong units. Bone growth progressed slowly.

This child is now 6 years 9 months old. Her physical appearance is that of a normal child, somewhat stunted in growth. The short stature is believed to be an inherited characteristic, since both parents are very short. Psychometric tests show an intelligence quotient of 59.

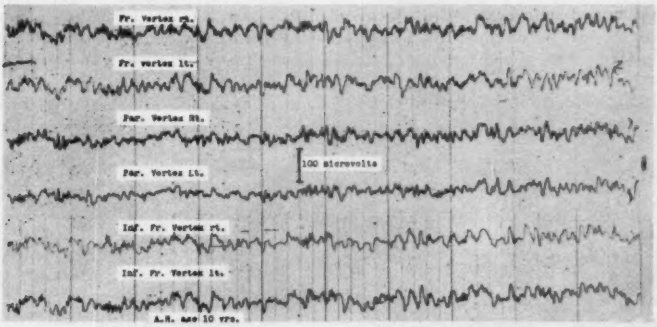

Fig. 1 (case 1).—Electroencephalographic tracings showing diffuse cerebral dysfunction (intelligence quotient, 50).

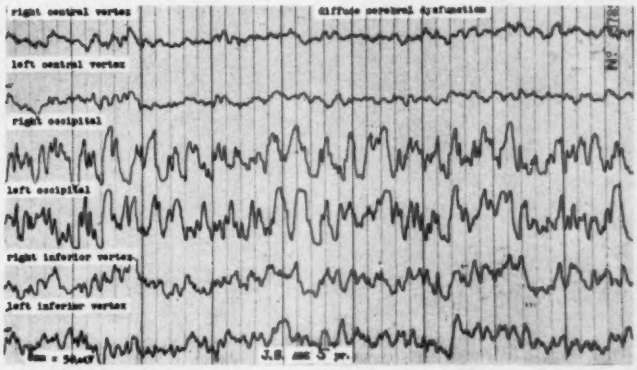

Fig. 2 (case 2).—Electroencephalographic tracings showing diffuse cerebral dysfunction (intelligence quotient, 59).

In spite of adequate treatment for almost five years, the child continues to function on a mentally defective level. Electroencephalographic studies indicate diffuse cerebral dysfunction (fig. 2).

Here again is seen the importance of direct investigation of the brain to ascertain whether a cerebral defect explains the lack of mental progress in a cretin in spite of adequate treatment.

CASE 3.—S. L., a while girl, was first seen at the Growth and Development Clinic at the age of 10 years. The child's condition had been diagnosed as cretinism at the age of 3 months at another institution, and she had received treatment since that time. Her record showed an intelligence quotient of 50 shortly before her appearance at the clinic. The child was well developed, and her bone age corresponded to her chronological age. Therapy was interrupted for

one month. At the end of this time, the child had put on considerable weight. Her serum cholesterol was 500 mg. per 100 cc. Therapy was resumed, and three weeks later the cholesterol dropped to 250 mg. per 100 cc.

The girl is now 13 years old. She is exceedingly well developed physically. She has matured sexually. Psychometric tests, performed at the age of 12, and again at 13, showed an intelligence quotient of 60. She functions mentally on a defective level and will probably continue to do so, since electroencephalographic studies repeatedly have shown diffuse cerebral dysfunction (fig. 3).

CASE 4.—P. B., an Italian boy, was first seen at the Growth and Development Clinic at the age of 5 years. The child's condition had been diagnosed at another institution at the age of 10 months, and he had received adequate treatment regularly.

When first seen at our clinic, the child was physically normal and his skeletal maturation was adequate. When therapy was interrupted for one month, the serum cholesterol was found to be

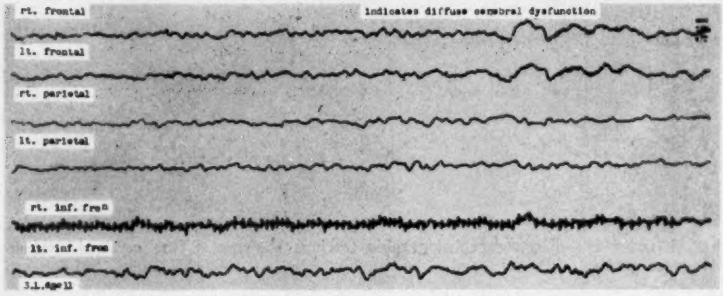

Fig. 3 (case 3).—Electroencephalographic tracings showing diffuse cerebral dysfunction (intelligence quotient, 60).

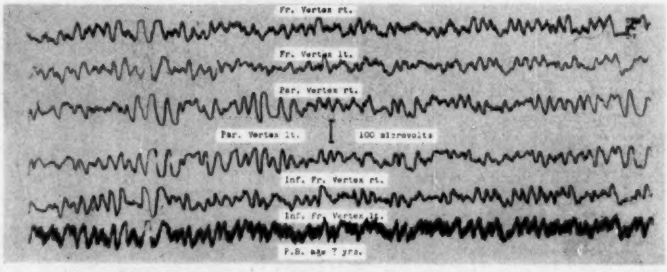

Fig. 4 (case 4).—Electroencephalographic tracings showing diffuse cerebral dysfunction (Rorschach test showed patient to be "functioning on a defective level").

920 mg. per 100 cc. This dropped to 320 mg. per 100 cc. after thyroid administration had been resumed for three weeks.

The child is now 8 years 9 months of age. Psychometric tests showed significant discrepancies. On the Stanford-Binet verbal tests the boy performed on a normal level (intelligence quotient of 91). His performance tests showed an intelligence quotient of 72. On the Rorschach test he gave responses which indicated the presence of a schizophrenic process. His Gestalt figures were indicative of severe emotional disturbance and the possible presence of a psychotic process. "The total patterning of the tests shows the patient as functioning on a defective level which is the result of an organic involvement and/or psychosis." Electroencephalographic studies indicated diffuse cerebral dysfunction (fig. 4).

CASE 5.—T. L.'s condition was diagnosed as cretinism at the age of 7 months at another institution. She was adequately treated. She first came to the clinic at the age of 7 years. At

that time she was physically well developed; her bone age was normal. Her mental age at this time, however, was only 3½ years, with an intelligence quotient of 49. When therapy was interrupted for one month, the cholesterol rose to 370 mg. per 100 cc. and dropped to 180 mg. per 100 cc. after resumption of thyroid administration.

The child is now 15 years old. She has matured normally. Repeated psychometric tests show an intelligence quotient of 45. Electroencephalographic studies reveal diffuse cerebral dysfunction (fig. 5).

These first five cases are similar in that the present level of mental development is within a defective range, in spite of the fact that therapy has been adequate. Physical, skeletal and sexual development are normal, but the children are all mentally retarded.

Electroencephalographic studies in all show diffuse cerebral dysfunction and explain why mental development has not kept pace with somatic growth.

CASE 6.—A. B., a white female infant, had been given thyroid since the age of 7 months. At the age of 4 years interruption of therapy revealed a serum cholesterol level of 350 mg. per

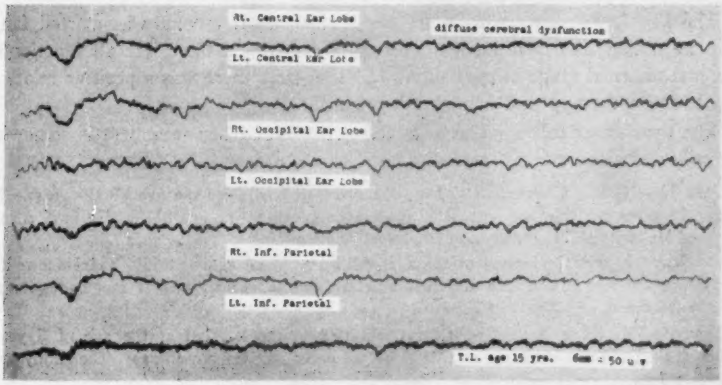

Fig. 5 (case 5).—Electroencephalographic tracings showing diffuse cerebral dysfunction (intelligence quotient, 45).

100 cc., with a decrease to 180 mg. per 100 cc. after resumption of therapy. The child was graduated from elementary school. She learned typing and worked for several years as a typist and was slow but accurate.

She is now 29 years old. She is married and has a normal 5 year old child. Psychometric tests show an intelligence quotient of 87. She functions within a low normal mental level. She attends to her household and maternal duties adequately, is socially well adjusted and has an understanding of her personal shortcomings.

CASE 7.—H. C., a white girl, had been given thyroid therapy since the age of 6 months. She first appeared at the clinic at the age of 11 years. At that time she seemed to be normal physically but somewhat retarded in growth. Her bone age was normal. Interruption of therapy was followed by a rise in cholesterol to 380 mg. per 100 cc., with a fall to 170 mg. per 100 cc. on resumption of thyroid treatment.

The patient was graduated from high school at the age of 19 years. She took courses at Hunter College, New York, and other schools. She is now 35 years old. She holds a position as clerical assistant. Her sexual development is normal. Psychometric tests performed at Hunter College a few years ago revealed an intelligence quotient of 112. She is somewhat shy but fairly well adjusted and happy.

CASE 8.—S. A. was admited to the hospital at the age of 2 months, with a history of attacks of dyspnea. A roentgenogram of the chest showed enlargement of the heart, probably due to myxedema. Roentgenograms of the bones showed the absence of epiphyses at the distal ends of the femurs and the proximal ends of the tibias (characteristic of cretinism). There were no carpal centers. The cholesterol was 180 mg. per 100 cc. The child was immediately given thyroid therapy. There was a striking change in appearance and in bone growth.

The patient is now 7 years old. She goes to school in a regular class. Her appearance is entirely normal. She is well grown. Psychometric tests showed an intelligence quotient of 110 a few months ago.

CASE 9.—M. L., a female Italian patient, has been receiving thyroid since the age of 7 months. Treatment has been adequate and continuous except for a short interruption for cholesteral tests. The level after withdrawal of therapy was 310 mg. per 100 cc., and this fell to 170 mg. per 100 cc. after resumption of thyroid administration. The child was graduated from grade school, attended a vocational high school and subsequently worked as a typist and as a waitress.

The patient is now 25 years old. She is married, runs her household competently and is socially well adjusted. She appears entirely normal. Psychometric tests performed a short time ago revealed an intelligence quotient of 89. Electroencephalographic studies revealed an entirely normal pattern.

The last four cases recorded are similar in that treatment was started fairly early in infancy and continued uninterruptedly. The patients are all functioning within the normal range of mentality. In these cases there was a positive relationship between therapy and mental achievement.

The three cases following seem to show that even when treatment is somewhat delayed cretins can attain a normal mental level.

CASE 10.—M. W., a white youth, has been given thyroid since the age of 1½ years. He is now 18 years old. He was graduated from high school at the age of 18. He is physically advanced for his age and sexually mature.

Psychometric tests performed at the age of 13½ and and again at 16½ years showed an intelligence quotient of 99. He is functioning within the normal mental range, despite the delay in treatment.

CASE 11.—M. R., a Spanish girl, was admitted to the hospital at the age of 3 years. Although the child was obviously retarded, she had never received any therapy. The family were Spanish refugees.

A roentgenogram of the carpal centers showed a bone age of 1 year. Her cholesterol was 350 mg. per 100 cc. and alkaline phosphatase 10.5 King-Armstrong units. She could not stand unsupported. Psychometric tests showed an intelligence quotient of 60.

When thyroid therapy was instituted, the child responded clinically, but her bone development lagged somewhat. Cholesterol fell to 165 mg. per 100 cc.; the alkaline phosphatase rose to 29 King-Armstrong units.

The patient is now 15 years old. She is physically well developed, although somewhat stunted in growth. This is believed to be a family characteristic, since the mother's height is under 5 feet (152 cm.). Bone and sexual maturation are normal. Psychometric tests showed an intelligence quotient of 90 in spite of delayed treatment.

CASE 12.—B. P., a white boy, was brought to the clinic at the age of 2 years 9 months. The child showed the typical signs and symptoms of congenital hypothyroidism (fig. 6). The bone age was retarded; there were no teeth as yet; the child could not stand unsupported, nor did he talk. Thyroid therapy was instituted. The clinical change was dramatic.

The patient is now 21 years old. In 1946 he was classified 1A by a Selective Service Board, showing that his condition was entirely unrecognizable. Psychometric tests disclosed the following results: At the age of 5 years 7 months the intelligence quotient was 70, at 17 years it was 87 and at 19 it was 92.

The boy had special educational aids at school for a speech defect (stammering) and was graduated from high school at the age of 19 years (fig. 7). He won a medal for clay modeling.

The patient now works in his father's dental laboratory. He is sexually and socially well adjusted. Electroencephalographic studies show an entirely normal brain pattern. In spite of greatly delayed treatment, the patient functions within a normal level of intelligence.

In the last three cases, although therapy was delayed until 1½ to 3 years of age, the mental results have been satisfactory. However, the next case shows the tragedy of delaying treatment too long.

Fig. 6 (case 12).—Appearance of patient before treatment at 2 years 9 months of age.

Fig. 7 (case 12).—Appearance of patient at the age of 19.

CASE 13.—F. K., a white girl 12 years of age, was admitted to the hospital with the typical clinical picture of cretinism. Her height was 94 cm. Basal metabolism tests showed an oxygen consumption of 425 calories, — 39 per cent. Cholesterol was 685 mg. per 100 cc. The bone age was on a 5 to 6 year level. The intelligence quotient was 36 per cent. The child sat up at 2½ years; her first tooth appeared at 3 years, and she walked at the age of 5 and talked at between 6 and 7

years. She had never received any thyroid. When therapy was instituted, the girl showed almost immediate striking changes. The basal metabolism rose to 912 calories. The cholesterol fell to 140 mg. per 100 cc.; the hemoglobin concentration, which had been 67 per cent on her admission, rose to 75 per cent.

The child was seen at irregular intervals in the clinic. In the next three years her height increased to 125 cm. (an increment of 31 cm.). She lost the clinical characteristics of the cretin, although she remained stunted in growth. At the age of 17 her height was 139 cm. Her hands and feet remained blunt and broad; her legs were unusually short in proportion to the trunk. Her dentition and bone age, however, were normal at this time. Her intelligence quotient remained within the defective range.

The patient was admitted to Letchworth Village school, at the age of 17½, where she remained for about a year and then was discharged to the custody of her mother. Physical examination at the time of discharge showed the patient to be "well built and well nourished. Results of respiratory, cardiovascular, abdominal, gastrointestinal and genitourinary examinations were normal. The nervous and glandular systems were essentially normal. Skeletal abnormalities suggested glandular disturbance. On the Stanford-Binet test her score indicated an intelligence quotient of 41, placing her in the high grade imbecile group of mental defectives."

Unfortunately, electrophysiology of the brain was in its early infancy at the time this patient was observed (she was lost track of in October 1937). Electroencephalographic studies would undoubtedly have shown a cerebral defect because of the long-standing lack of thyroid.

The case that follows shows that, while early therapy is important, adequate therapy is just as important.

Case 14.—M. B., a white girl, was brought to my attention at the age of 6½ years. The mother had a history of hypothyroidism during this pregnancy. The condition of the child had evidently been diagnosed as cretinism at the age of 4 months, and she had been given thyroid. The dosage, however, had been entirely inadequate. The child received 1/10 grain (6 mg.) daily; this was increased to 2/10 grain (12 mg.) daily and finally to 3/10 grain (18 mg.) at the age of 6 years. For some reason therapy had been omitted entirely during the summer months.

At the age of 6½ years the child was 38 inches (97 cm.) tall and weighed 35 pounds (16 Kg.). She did not give the appearance of a cretin at this time, but her bone age was on a 6 month to 1 year level. Her intelligence quotient was 78. The cholesterol was 295 mg. per 100 cc.

The dose of thyroid was immediately increased to 1 grain (60 mg.), then to 2 grains (130 mg.). In the succeeding six months the child grew 5 inches (13 cm.). A roentgenogram of the carpal bones showed the addition of two new centers. Mental tests revealed a four months' growth on the Stanford-Binet scale; prognosis for continued mental development seemed to be favorable.

The child is now 11½ years old. She is taking 3 grains (190 mg.) of thyroid daily. She is 53 inches (135 cm.) tall and weighs 74 pounds (33.6 Kg.). Her bone age is just beginning to approximate her chronological age. Her intelligence quotient shows that the child is still functioning at the low borderline of normal intelligence.

It would be most important here to have electroencephalographic studies made in order to be able to venture a prognosis for future mental progress, but the family, who live in a distant city, have not consented to such studies.

Case 15.—L. C., a white female infant, was admitted to the hospital at the age of 6 months. A diagnosis was made on the basis of the typical clinical picture of cretinism and the absence of ossification centers at the tibia and femur. The father was unknown; the mother was mentally defective. The cholesterol was 400 mg. per 100 cc. and alkaline phosphatase 8 King-Armstrong units. Gesell developmental tests showed a grossly retarded behavior pattern with a defective quality to the response. It approached most closely that of a neonatal infant, but there were a few motor responses of about 6 to 16 weeks.

Thyroid therapy was started. In nine days the cholesterol dropped to 220 mg. per 100 cc.; the alkaline phosphatase rose to 24 King-Armstrong units. The infant lost her cretinoid look. She was placed in a foster home. At the age of 1 year she was readmitted for evaluation of therapy. At this time the bone age was consistent with the chronological age; the cholesterol was

120 mg. per 100 cc., showing that therapy had been adequate. Gesell tests made at this time showed an adaptive behavior at the 24 week level.

At the age of 17 months the child was retested, and, although she was physically normal, her developmental quotient was again on the defective level of 54 weeks.

The child is now at the Willowbrook State School for mentally retarded children. She is 3 years old. The outlook, of course, is unfavorable because of the poor family history and the lack of mental progress even with adequate therapy.

Electroencephalographic tests have been attempted several times but had to be abandoned because of lack of cooperation in spite of sedation. I hope to have these tests attempted again very soon.

The association of epilepsy and glandular defects, notably hypothyroidism, has been previously reported.[22] The next two cases are of children who have never

Fig. 8 (case 14).—Roentgenogram taken at chronological age of 6½ years showing the bone age to be 6 months to 1 year.

given a history of seizures, nor could any family history be elicited. Both, however, show electroencephalographic tracings which indicate an epileptic pattern.

Case 16.—J. T. had been given thyroid since the age of 21 months. At that time, her bone age was retarded and her cholesterol was found to be 285 mg. per 100 cc. The mother had always had a low basal metabolic rate, and one other member of the maternal family was being treated for hypothyroidism. One male sibling had cerebral palsy.

The child was first seen by me at the age of 4 years 3 months, when her own physician joined the United States Medical Corps.[23] At this time, her physical stature and skeletal maturation were entirely normal. The cholesterol level was 150 mg. per 100 cc., evidence of adequate treatment.

This child has been observed closely. She is now 10½ years old. Psychometric tests have been applied as follows: At the age of 4 years 3 months the intelligence quotient was 70, at 6 years 8 months it was 82, at 9 years 1 month it was 108 and at 10 years it was 111. The child

22. Dana, C. L.: Text-Book of Nervous Diseases, for the Use of Students and Practitioners of Medicine, ed. 10, New York, William Wood & Company, 1925, p. 511.

23. Dr. Carl Zelson permitted me to follow this case closely.

now functions within the range of high normal mentality. Her intelligence quotient during the past six years shows an increment of 41 points. Electroencephalographic studies revealed "numerous diffuse and symmetrical bursts of 3 to 6 per second activity lasting as long as 5 seconds. It is a type commonly seen in idiopathic epilepsy" (fig. 9).

CASE 17.—P. W. differs from all the others in the group in that he developed apparently normally up to the age of 4 years.

At the time of his admission to the hospital, he was 5 years old. The mother stated that he had had an unusually stormy infancy. He had repeated attacks of croup, otitis media and infections of the upper respiratory tract. He had had measles and whooping cough, both quite severe. He had been subjected to tonsillectomy and adenoidectomy at the age of 2 years.

On his admission the patient presented a clinical picture of mild hypothyroidism. His skin was puffy and pasty; his tongue protruded. Cholesterol was 245 mg. per 100 cc. and total blood lipids were 1,480 mg. Roentgenograms of the wrists showed the presence of only two carpal centers. He was 98 cm. tall. His basal metabolism was 500 calories per 24 hours.

Thyroid administration was started. His basal metabolism rose to 864 calories. His cholesterol decreased to 190 mg. per 100 cc.

The boy has been treated continuously to the present. He is 15 years old. He is 139 cm. tall. His sexual maturation and bone growth are entirely normal. He is somewhat stunted in growth,

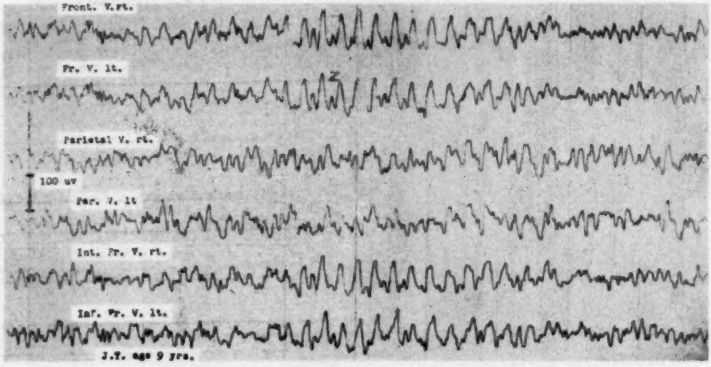

Fig. 9 (case 16).—Electroencephalographic tracings showing pattern commonly seen in idiopathic epilepsy (intelligence quotient, 111).

which may be in part a family trait; his epiphyses are still, however, wide open, showing further growth potentiality. In addition to his other handicaps, the boy suffers from a chronic asthmatic condition and attacks of tracheobronchitis. The patient is a serious boy. He is keenly aware of his stunted size. He has been in a health improvement class for the past eight years and is receiving remedial help in reading and psychiatric counseling.

Psychometric tests performed at the age of 8 years 8 months showed the intelligence quotient to be 87. Tests at 14½ years of age revealed it to be 94. Electroencephalographic studies on two occasions showed some bursts as seen in idiopathic epilepsy.

Although, at present, both children (cases 16 and 17) are functioning within the normal range of intelligence, prognosis will have to be guarded because of the epileptic tracings shown by the electroencephalographic studies.

The next two cases demonstrate how electroencephalographic studies can be used in making a prognosis of mental development.

CASE 18.—S. G., a white male infant, was seen by me at the age of 14 months. He had been given thyroid therapy since the age of 4 months. The dosage had been somewhat inadequate, as shown by some retardation in bone age and some delay in development. The child could neither

crawl nor stand unsupported. He appeared to be somewhat myxedematous. Cholesterol was 275 mg. per 100 cc. Psychometric tests at this time showed a developmental quotient of 50. The electroencephalogram, however, showed an entirely normal pattern. Because of this, I felt that the prognosis was good.

The dose of thyroid was increased to 1½ grains (0.09 Gm.) daily. Within two weeks the mother reported that the child stood alone and was beginning to try to take a few steps. His cholesterol dropped to 200 mg. per 100 cc. Two months later the child began to propel himself on a kiddy car.

The thyroid dose was increased to 2 grains (0.13 Gm.) daily. The child continued to progress. Psychometric tests repeated at the age of 24 months showed a developmental quotient of 80, an increment of 30 points.

Case 19.—H. W., a white male infant 2 months of age, was admitted to the hospital. He showed the obvious picture of congenital hypothyroidism. His ossification centers in the tibias and femurs were absent; carpal centers were also absent. Cholesterol was 240 mg. per 100 cc.;

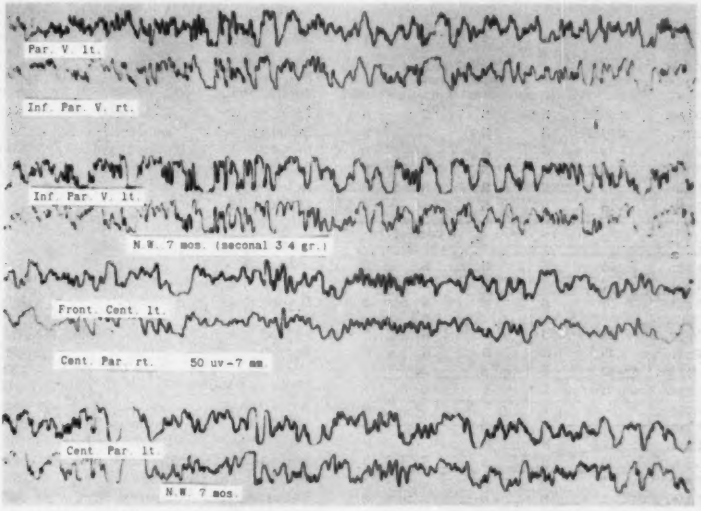

Fig. 10 (case 19).—Electroencephalographic tracings showing normal pattern.

alkaline phosphatase was 24 King-Armstrong units. An electroencephalogram showed a normal brain pattern.

Treatment was started with thyroid. Within one month there were two carpal centers, and within four months the centers in the tibias and femurs had attained remarkable growth. In view of the early onset of treatment and the normal brain tracings, the outlook for mental progress seemed favorable.

Unfortunately, this infant has had to contend with an unwholesome parental attitude. The parents have decided to separate and are anxious to place the infant in an institution. For this reason, I have never been convinced that they gave the child adequate attention or even the adequate therapy advised. The child was readmitted to the hospital at the age of 8 months after six months of treatment. At this time his cholesterol level was 340 mg. per 100 cc., which spoke for inadequate therapy. Gesell tests at this time showed development at the 20 to 24 week level. The electroencephalogram was again entirely normal. The problem was discussed with the parents, and they promised to keep the infant a while longer.

At 14 months the child was again tested, and his development was at the 28 to 36 week level. At 21 months his behavior pattern was found to be at the 40 to 52 week level; at 2 years of

age he had progressed to the 68 to 72 week level. The electroencephalogram at this time was again entirely normal.

The steady increment in the developmental quotient in spite of parental rejection and the fact that there is no cerebral impairment as shown by repeatedly normal electroencephalographic tracings should give a good prognosis for future mental progress. The outlook is, however, not too good, since the parents have definitely decided to institutionalize the child. A wholesome parental attitude is a significant factor in the mental progress of cretins.

CASE 20.—D. K. has been receiving thyroid since the age of 9 months. She was first seen at the clinic at the age of 7 years. On withdrawal of therapy the cholesterol was 300 mg. per 100 cc., and this fell to 150 mg. per 100 cc. after thyroid administration was resumed. The child has developed well physically. Her skeletal and sexual maturation are normal. Psychometric tests made at the age of 7 years 1 month showed an intelligence quotient of 75; at 10 years 10 months

TABLE 1.—*Results Observed on Therapy in a Group of Cretins*

1 Case No.	2 Age at Onset of Therapy	3 Present Age, Yr.	4 Adequacy of Therapy	5 Physical Development	6 Sexual Development	7 Skeletal Development	8 Mental Development, Terman Scale	9 Electroencephalogram	10 Cholesterol Level Before Therapy, Mg./100 Cc.	11 Cholesterol Level After Therapy, Mg./100 Cc.
1	15 mo.	11-10/12	S *	S	S	S	Defective	Abnormal	285	200
2	2 yr.	6-9/12	S	S	..	S	Defective	Abnormal	300	220
3	3 mo.	13	S	S	S	S	Defective	Abnormal	500 w †	250
4	10 mo.	8-9/12	S	S	..	S	Defective	Abnormal	920 w	320
5	7 mo.	15	S	S	S	S	Defective	Abnormal	370 w	180
6	7 mo.	30	S	S	S (married; has a normal child)	S	Dull normal	.....	350 w	180
7	6 mo.	35	S	S	S	S	High normal	.....	330 w	160
8	2 mo.	7	S	S	..	S	Normal	.....	180	180
9	7 mo.	28	S	S	S (married)	S	Dull normal	Normal	310 w	170
10	1½ yr.	18	S	S	S	S	Normal	.....	...	180
11	3 yr.	15	S	S	S	S	Normal	Normal	350	165
12	2-9/12 yr.	21	S	S	S	S	Normal	Normal	280	200
13	12 yr.	18	U *	U	U	S	Defective	.....	685	140
14	4 mo.	11½	U	S	..	S	Borderline	.....	295	160
15	6 mo.	3	S	S	..	S	Defective	Unsuccessful	400	220
16	21 mo.	10½	S	S	..	S	High normal	Epileptic pattern	285	160
17	1 yr.	15	S	S	S	S	Normal	Epileptic pattern	295	180
18	5 mo.	2	S	S	..	S	Normal	Normal	276	180
19	2 mo.	2	S	S	..	S	Dull normal	Normal	240	240
20	9 mo.	12	S	S	S	S	Defective	Unusually mature	300	160

* S signifies satisfactory and U unsatisfactory.
† Levels marked w are those determined after thyroid therapy was withdrawn.

the quotient was 65, at 11 years 7 months it was 60 and at 12 years it was also 60. In spite of the early onset and adequacy of therapy, the child remains mentally defective.

Electroencephalographic studies made on this child at the age of 10½ years showed an "unusually mature pattern for this age." Again at 11½ years "the frequency of the alpha waves is faster than in the previous record and shows still further maturing." Dr. Strauss could not explain why this child should show such an unusually mature electroencephalographic pattern.

RESULTS WITH COMMENT

Table 1 summarizes the significant data in all cases. The age at which therapy was started can be seen in column 2 of the table; the present age, or the age when the patient was last seen, is recorded in column 3. Column 4 describes the treatment as satisfactory (S) or unsatisfactory (U). Treatment was considered satisfactory if continued in proper dosage from the onset of therapy. Proper

dosage was checked against clinical effect, roentgenographic estimate of bone maturation and cholesterol level. For F. K. (case 13) no therapy can be regarded as satisfactory, since the diagnosis was delayed until the age of 12 years. M. B. (case 14) cannot be considered to have had satisfactory treatment, since she had a history of inadequate dosage since infancy, and at the age of 6½ years the bone age was only 6 months to 1 year. It is questionable whether H. W. (case 9) received adequate therapy, but, since the roentgenographic appearance of the bones and the cholesterol level are normal and the mental progress is good, I have called his treatment satisfactory in spite of the unwholesome parental attitude.

It can be seen from column 5 that, with the exception of F. K. (case 13), all the cretins attained satisfactory physical development irrespective of whether treatment was started at 2 months or at 3 years. All these children eventually attained a height which conformed to normal expectations, familial and hereditary variations being taken into account. As far as physical results are concerned, thyroid therapy has been most gratifying.

Satisfactory sexual maturation (column 6) proceeded without delay in all patients in whom it was expected. Two of the patients, A. B. and M. L. (cases 6 and 9), are married; the former has a normal child 5 years of age.

Skeletal maturation (column 7) based on Todd's standards [24] was eventually satisfactory in all patients.

Briefly, it can be stated that there was good correlation between thyroid therapy and physical, skeletal and sexual development in all the children.

Since Epstein and Lande [25] first called attention to the relation of serum cholesterol to the basal metabolism, there has been much discussion concerning reliability of using fluctuations in the levels of the blood lipids as diagnostic aids in hypothyroidism.[26]

Several authors have stressed total serum lipids as the best indication of hypothyroidism. Other observers have preferred to use the level of the serum cholesterol. That there is an elevation of the blood lipids, notably the cholesterol, in hypothyroidism has been noted by many observers. My own experience generally conforms to this concept, except that in the young untreated cretins the total cholesterol was occasionally found to be within normal limits (column 8).

The level of cholesterol in the treated children with hypothyroidism, however, after withdrawal of thyroid therapy, was more significant. There was invariably an increased serum cholesterol, which dropped after resumption of treatment with thyroid (column 8, cases marked w). Wilkins [27] has emphasized this withdrawal rise in cholesterol as a confirmation of hypothyroidism.

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24. Todd, T. W., and others: Atlas of Skeletal Maturation, St. Louis, C. V. Mosby Company, 1937.

25. Epstein, A. A., and Lande, H.: Studies on Blood Lipoids: Relation of Cholesterol and Protein Deficiency to Basal Metabolism, Arch. Int. Med. **30**:563 (Nov.) 1922.

26. Mason, R. L.; Hunt, H. M., and Hurxthal, L. M.: New England J. Med. **203**:1273, 1930. Hurxthal, L. M.: Blood Cholesterol and Thyroid Disease: Myxedema and Hypercholesteremia, Arch. Int. Med. **53**:762 (May) 1934. Radwin, L. S.; Michelson, J. P.; Melnick, J., and Gottfried, S.: Blood Lipid Partition in Hyperthyroidism of Childhood, Am. J. Dis. Child. **60**:1120 (Nov.) 1940. Gildea, E. F.; Man, E. B., and Peters, J. P.: J. Clin. Investigation **18**:739, 1939. Sperry, W. M.: J. Biol. Chem. **117**:391, 1937. Gortz, S.: Acta pædiat. **29**:553, 1937.

27. Wilkins, L.: J. Pediat. **12**:429, 1938.

Column 9 of table 1 shows the mental level of this group of cretins according to the Terman classification (table 2).

It may be seen that of all 20 patients, eight have remained mentally defective and one functions within the borderline of normal intelligence, while 11 have attained normal intelligence, two in fact being within the superior normal range.

When the two children are excluded whose treatment was unsatisfactory, it is seen that seven, or 39 per cent, have remained definitely feebleminded, in spite of adequate treatment. That these results are not correlated to the onset of therapy can be seen from column 2 of table 1. Certainly in these seven mentally defective children, there is a gross discrepancy between therapy and mental progress.

It seemed to me that if this discrepancy could be explained by cerebral impairment direct investigation of the brain might reveal such impairment. Accordingly, electroencephalographic studies were made in these seven cretins and, as a control, in six of the cretins who are mentally normal. All the latter showed brain patterns which are entirely consistent with normal mentality. Of the seven feebleminded cretins, however, one infant did not cooperate, one child showed a peculiarly unusual maturity of brain waves on repeated tests and five cretins (80 per cent) showed diffuse cerebral dysfunction. These numbers are small, but the results

TABLE 2.—*Mental Levels Attained by Cretins According to the Terman Scale of Intelligence Quotients*

Range of Intelligence Quotients	Category	All Patients	Adequately Treated Patients	Onset of Therapy
Below 70	Definite feeble-mindedness	8	7	3 mo. to 2 yr.
70 to 79	Borderline	1	0	4 mo.
80 to 89	Dull normal	2	2	7 mo.
90 to 110	Normal	7	7	2 mo. to 3 yr.
Over 110	High normal	2	2	2 mo. to 21 mo.

seem to be more than fortuitous and certainly indicate that further similar studies should be made.

Up to a few years ago, progress in the knowledge of cerebral processes was handicapped by an absence of methods of studying the intact brain. But since the discovery that methods of electrophysiology can be applied to living brain tissue, it seems logical to use these methods in clarifying the knowledge of the mentality of congenital hypothyroidism, about which there has been so much discussion.

In 1937 Kreezer wrote of distinctive electroencephalographic patterns in certain types of mentally deficient persons, notably mongolian idiots, hydrocephalic children, persons with phenylpyruvic amentia and a few cretins. Other authors have reported that metabolic disturbances altered the pattern of the electroencephalogram.[28] These authors believed that there was a correlation between the rate of oxidation of brain cells and the frequency of alpha waves. Variations in the rate of oxidation of brain cells led to a reduction in alpha frequency. That

28. Lindsley, D. B., and Rubenstein, B. B.: Proc. Soc. Exper. Biol. & Med. **35**:558, 1937. Rubin, M. A.; Cohen, L. H., and Hoagland, H.: Endocrinology **21**:536, 1937. Jasper, H. H., and Andrews, H. L.: Electro-Encephalography: Normal Differentiation of Occipital and Precentral Regions in Man, Arch. Neurol. & Psychiat. **39**:96 (Jan.) 1938. Ross, D. A., and Schwab, R. S.: Endocrinology **25**:75, 1939. Gant, W. H., and Fleischmann, W.: Am. J. Psychiat. **104**:673, 1948.

there is a reduced rate of oxidation in the brain tissue of cretins is borne out by several studies of Himwich,[29] who recorded that the arteriovenous oxygen of the brain cells of cretins is 7 volumes per cent lower than that in normal brain tissue. After thyroid therapy, he demonstrated an average increase of 32 per cent in brain metabolism.

Whether changes in the electroencephalogram can be related to thyroid deficiency in the absence of organic cerebral disturbance is, at present, highly speculative. It seems logical, however, to hypothesize an organic cerebral disturbance in some persons with congenital hypothyroidism, and in five of the present series of feebleminded cretins such organic disturbance was actually seen from the brain tracings.

It seems to me that these studies should suggest a new approach to the investigation of the mental deficiency associated with cretinism. As Gesell has pointed out, the developmental maturity of the cretin can be appraised by studying his behavior patterns at intervals. The initial maturity level and the change in this level with therapy are important in prognosticating his final mental status. It seems to me that electroencephalographic studies associated with behavior studies will give added valuable information toward the making of a prognosis of the potential mental attainments of the cretin.

SUMMARY

There is considerable evidence to show a lack of correlation between mental results obtained in the child with congenital hypothyroidism and adequacy of therapy. This discrepancy is ascribed to such causes as the degree of deficiency of the gland, the innate mental endowment and—what seems to be the most significant factor—an impairment of the brain, existing in the cretin either as a primary amentia or as a developmental result of lack of thyroid stimulation.

In a group of cretins followed for periods varying from one to 25 years, psychometric tests showed that seven, or 39 per cent, of these patients have remained mentally defective in spite of adequate treatment.

In an effort to investigate a possible cerebral defect in these patients, electroencephalographic studies were made. Five of these cretins (80 per cent) showed electroencephalographic tracings that revealed "diffuse cerebral dysfunction." Electroencephalographic studies made as a control in six of the cretins who had reached a normal level of intelligence showed tracings that were entirely consistent with normal mentality.

So far only 13 cretins have been studied from this angle. Although the number is small, I believe the results to be significant and tentative conclusions may be drawn as follows: 1. That a cerebral defect explains the mental deficiency of adequately treated cretins can be proved by direct investigation of the brain by the electroencephalogram. 2. When such studies are made in infancy, they can be of significant prognostic import, since no amount of thyroid can bring about normal mentality in the presence of cerebral dysfunction, whereas if the electroencephalogram shows a normally functioning brain, adequately pursued therapy can bring about normal mentality even in congenital hypothyroidism.

The electroencephalographic tests were applied and readings interpreted by Dr. Hans Strauss.

29. Himwich, H. E.; Dale, C.; Fazenkas, J. F., and Herrlich, H. C.: Am. J. Psychiat. **98**: 489, 1942.

Case Reports

HERNIA OF UTERUS, OVARIES AND TUBES IN A SIX WEEK OLD INFANT

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AND
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To the surgeon and pediatrician hernia of infancy is of considerable importance. The condition is rather common, occurring in both male and female infants. The hernia may appear early in infancy as a small swelling in the groin or later when the crying and straining become more vigorous. This congenital lesion occurs less frequently in girls than in boys; in them during the development and attachment of the round ligament there is a process of peritoneum accompanying it down through the inguinal canal which is similar to the processus vaginalis peritonali in boys, but is known as the canal of Nuck. This canal normally closes off entirely and disappears, but it may persist and cause an inguinal hernia. In the female infant it is not uncommon to find an ovary present in the sac, which may become irreducible and partially strangulated. Hertzfeld,[1] Fuld,[2] Mac Lennan [3] and others have pointed out that strangulated hernia in infants is rare, yet numerous cases have been reported in the literature.[4] These authors stated that from 75 to 95 per cent of incarcerated hernias are reducible with the usual recommended procedures of sedation and anesthesia. The subject of incarceration and strangulation is one which is much debated. From these statements, without a clear interpretation of the terms strangulation and incarceration, one might develop a feeling of complacency about hernia in infancy. Occasionally one is called on to deal with a difficult hernia. Incarceration carries the threat of strangulation, and patients with it should be under constant supervision. There can be no rules, but if the patient lacks symptoms or signs of obstruction and the temperature and leukocyte count are not elevated conservative measures may be tried. These methods are aimed primarily at reducing the edema of the contents of the hernia and relaxing the musculature surrounding the hernial orifice. It is not considered safe to wait longer than five to six hours before proceeding with operation. Seventy to 80 per cent of patients with hernia can be successfully treated by conservative methods. In the remaining 10 to 20 per cent, in whom incarceration persists, one is more apt to find the unusual hernia, the differential diagnoses of which may be perplexing, and the true situation is determined only at operation.

In reviewing the literature while preparing to report a case of hernia of the uterus, ovaries and tubes it was found that such a case is apparently unusual, especially when one confines the review to its occurrence in infancy.

1. Herzfeld, G.: Hernia in Infancy, Am. J. Surg. **39**:422, 1938.

2. Fuld, J. E.: Strangulated Inguinal Hernia in Infants, New York M. J. **109**:233, 1919.

3. Mac Lennan, A.: The Radical Cure of Inguinal Hernia in Children, Brit. J. Surg. **9**:445, 1922.

4. Thorndike, A., Jr., and Ferguson, C. F.: Incarcerated Inguinal Hernia in Infancy and Childhood, Am. J. Surg. **39**:429-437, 1938.

Eisenhart [5] in 1885 made a thorough review of the literature and found only 12 cases of hernia of the uterus up to that time; none of the patients were infants. McMillan [6] in 1942 reviewed the literature and reported a case of hernia of the uterus. He found that only one author, Ludington,[7] in 1920, definitely recorded a case of the presence of the uterus in an indirect inguinal hernia in a child 19 months old. Watson [8] in 1946 collected the records, including his own, of 686 cases of hernia of the ovary, tube and uterus. One hundred and eighty of these cases were of infants and children under 1 year. Of the 180 cases, 12 were of hernia of the uterus, ovaries and tubes. The youngest patient was 1 week old; the ages of the remaining patients were two 2 months, one each 4, 6 and 9 months and six 1 year.

While cases like the following are rarely encountered, it seems worth while to report them and to call attention to such complications arising in the surgical problems of hernia in infants. As Sir Lancelot Barrington-Ward aptly stated, "The adult may safely be treated as a child but the converse can lead to disaster." [9]

REPORT OF CASE

M. L. G. was born prematurely on Feb. 16, 1949. The weight at birth was 4 pounds (1,800 Gm.). At 3 weeks a physician was consulted about a swelling the baby had in its left side. He gave the child several injections of penicillin and suggested that the swelling might have to be opened if it did not disappear.

The swelling failed to subside under this treatment, and a week later the child was seen by us. At 4 weeks of age the infant was found to have in the left inguinal region a hard nonreducible mass which was freely movable and could be moved up and down from the inguinal ring into the labia. At this time the infant experienced pain on pressure over the swelling, as evidenced by crying, but there were no signs whatsoever to indicate strangulation. The usual methods of reduction were without success. We were inclined to wait, since the child was taking her formula well, was not vomiting and in no way presented symptoms of strangulation from a possible hernia that had been present for three weeks. This decision was equally influenced by the fact that the baby weighed only a little over 5 pounds (2,270 Gm.). During the following two weeks the baby's status improved in that it gained about a pound (454 Gm.) in weight and had no symptoms referable to the hernia.

When the baby was 6 weeks old the swelling increased in size during a bout of crying and became tender to the extent that she would not tolerate a diaper without continuous crying. It was at this time that we seriously began to consider surgery, despite the fact that the baby still presented none of the usual signs of strangulation. In the succeeding five to six hours of deep sedation it was again impossible to reduce the mass. The baby continued to take her formula and did not vomit, and evacuation was normal. The abdomen was soft, and no obvious pain was elicited except that from pressure on the swelling itself. The following morning the infant was much more irritable but otherwise the same. Nevertheless, it was felt that surgery was necessary. With the area under a 0.5 per cent procaine hydro-

5. Eisenhart, H.: Fall von Hernia inguinalis cornu dextri uteri gravidi, Arch. f. Gynaek. **26**:439, 1885.

6. McMillan, W. M.: Unusual Viscera in Indirect Inguinal Herniae, Ann. Surg. **116**:266, 1942.

7. Ludington, N. A.: Case of Uterus and Both Ovaries in Indirect Inguinal Hernia Sac, New York M. J. **111**:986, 1920.

8. Watson, L. F.: Hernia, ed. 3, St. Louis, C. V. Mosby Company, 1948.

9. Barrington-Ward, L. E.: Treatment of Hernia in Children, Practitioner **133**:669, 1934.

chloride anesthesia, an incision about 3 cm. in length was made, and the hernia was exposed and isolated. When the sac was opened, the contents were found to be the uterus, the tubes and both ovaries. The uterus was twisted counterclockwise about 45 degrees, and there was a moderate congestion of the tubes and ovaries. It was necessary to give a brief ether anesthesia and to reduce the contents of the sac. The sac was then ligated high and removed. The round ligament was ligated and sewed into the corner of the wound. A modified Ferguson operation was then done, closing the canal completely by stitching the internal oblique muscle and the upper layer of the aponeurosis to Poupart's ligament and imbricating the external oblique over it. Cotton was the suture material used. The postoperative course was uneventful.

COMMENT

In females the differential diagnosis of incarcerated hernia may be difficult. In female children it is sometimes difficult to locate the external ring, and the hernia does not descend so readily nor so far as in male children. If it is irreducible, it almost always contains an ovary and a tube and in rare instances, the uterus. Hydrocele of the canal of Nuck, inguinal or femoral adenitis and new growth should be considered. Frequently, as mentioned before, the true situation is determined only at operation. Not every hernia will progress to strangulation with gangrene, but it is impossible to determine which one will result in strangulation. Undoubtedly subacute incarceration occurs in many cases in infancy; this, however, should not be held as a reason for delaying treatment. It is the experience of all that many hernias may be successfully treated by conservative measures, but when this is not accomplished with ease conservative measures become dangerous and illogical. The case presented was that of a child who for a period of about four weeks had an incarcerated hernia which probably contained one ovary. Two weeks later during a bout of crying the uterus was forced into the sac. A yarn truss to prevent any enlargement of the hernia was tried early, but any pressure more than that of a diaper made the child restless; hence its use was discontinued.

SUMMARY

The case of a 6 week old girl with a hernia of the uterus, tubes and ovaries is presented. Twelve cases of a similar nature in the literature are reviewed.

1109 State Street.

PYLORIC STENOSIS IN TWINS

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Pyloric stenosis in both twins of a set occurs very rarely. When the stenosis is present in both infants, they are usually of the monovular type. Laubscher and Smith,[1] in a review of the literature up to 1947, found only thirteen reported cases of monovular twins in whom pyloric stenosis had occurred. In eleven sets (84.6 per cent) both twins were affected. In the other two sets (15.4 per cent) one twin was affected. This rate of occurrence in both of a set of monovular twins is in marked contrast to the rate of occurrence in both twins when they are binovular in type. Of twenty-four sets of binovular twins reported by the same authors, pyloric stenosis occurred in both twins of only two sets (8.4 per cent), whereas in the remaining 22 sets (91.7 per cent) one of the twins was affected. It was Sheldon [2] who first noted that "when pyloric stenosis affects uniovular twins both infants show the condition" and "when pyloric stenosis affects binovular twins the disease is likely to occur only in one twin." He reviewed 1,000 cases of pyloric stenosis at the Hospital for Sick Children in London. In his series there were twenty-three sets of twins. In the only set known to be monovular, both twins were affected. In each of the remaining twenty-two sets, only one twin had the disease. In ten of these sets the type of twinning was unknown. The only other large group of cases was reported by Ford, Brown and McCreary,[3] who found that in a series of 436 children with pyloric stenosis there were twelve sets of twins. Nine of the sets were known to be binovular; two sets were monovular, and in one set the type of twins was unknown. In the two monovular sets, both twins had pyloric stenosis, whereas in the nine binovular sets only one member of the twins was affected.

The regularity with which both of monovular twins are affected suggests very strongly that a genetic factor is of great importance in the development of pyloric stenosis.

Because of its rarity and because it increases the evidence in favor of a genetic factor, we wish to report a case of pyloric stenosis occurring in both members of a set of monovular twins.

From the Departments of Surgery and Pediatrics, Michael Reese Hospital.

1. Laubscher, J. H., and Smith, A. M.: Pyloric Stenosis in Twins: Review of Literature and Report of Case, Am. J. Dis. Child. **73**:334 (March) 1947.

2. Sheldon, W.: Hypertrophic Pyloric Stenosis in One of Uniovular Twins, Lancet **1**:1048 (May 7) 1938.

3. Ford, N.; Brown, A., and McCreary, J. F.: Evidence of Monozygosity and Disturbance of Growth in Twins with Pyloric Stenosis, Am. J. Dis. Child. **61**:41 (Jan.) 1941.

REPORT OF A CASE

Larry and Jay V., twin boys, were born on Sept. 18, 1949 to a 25 year old primiparous woman. The pregnancy had been normal. The labor lasted six hours. The presentation of Jay, the first baby born, was cephalic, and he was delivered spontaneously. The second baby, Larry, was also delivered spontaneously by a breech presentation. Examination at the time of delivery showed that there was only one placenta. The membranes were, unfortunately, not dissected to observe the chorionic layer. At birth Jay weighed 6 pounds 8 ounces (2,950 Gm.) and Larry 5 pounds 14 ounces (2,665 Gm.). Both children were breast fed. They progressed normally and were discharged from the hospital on the eighth day. The record of the attending physician at the hospital states that they were identical, and their appearance and similarity of sex helps to confirm this opinion.

At two weeks of age, both babies began to vomit. They vomited about every third feeding. Thickened feedings were used, but the vomiting continued and gradually became projectile in nature. The vomitus was not bile stained. They entered the Sarah Morris Division of Michael Reese Hospital on October 16, at 4 weeks of age.

Physical examination showed both to be well developed and fairly well nourished white boys. Their color and hydration appeared good. The fontanels were normal in size and not depressed. There was no adenopathy present. The lungs were clear. The hearts were not enlarged, and there were no murmurs audible. On inspection of the abdomen, peristaltic waves could be seen passing across the upper portion of the abdomen from left to right in both infants. A small tumor mass could be palpated in the region of the pylorus in each infant. Roentenograms of the stomachs showed an elongated and narrow pylorus present in both babies. A diagnosis of pyloric stenosis was made, and on October 20 it was decided that an operation would be necessary. At this time Jay weighed 6 pounds 15 ounces (3,147 Gm.) and Larry 6 pounds 12 ounces (3,062 Gm.).

Accordingly, adequate quantities of isotonic sodium chloride solution and dextrose in distilled water were administered subcutaneously, and on October 21 a vein at the ankle was isolated and a cannula placed in it. Seventy-five cubic centimeters of plasma was administered to each infant, and they were typed and cross matched for transfusion. The next morning the stomach of each was washed out and a no. 10 French catheter left in the stomach. Atropine, 1/800 grain (0.075 mg.), was given subcutaneously, and the patients were taken to the operating room.

In each infant a hickory-nut-sized, typical pyloric tumor was exposed at operation. The only difference in the two tumors was that the second one (from Larry) was more elongated and had a slightly irregular surface. The usual Fredet-Rammstedt type of operation was performed.

In the immediate postoperative period each received a transfusion of 75 cc., and feedings were begun at the end of twelve hours. Jay retained his oral feedings well, and on October 24 his temperature was 97.2 F. and his respiration rate 32. His abdomen was soft, and he appeared to be in excellent condition. On October 26, he had a formed stool. His weight at this time was 7 pounds 1 ounce (3,204 Gm.). Larry, however, did not retain his feedings well, and three days after the operation he was regurgitating a good deal. This necessitated continued intravenous therapy to maintain his electrolyte and water balance. On October 25, he had a sudden episode of unexplained cyanosis, and a second transfusion of 70 cc. of blood was given. On the fifth postoperative day he passed two formed stools. He began to retain oral feedings then, and by November 1 was retaining all feedings without any vomiting. Both babies were discharged on November 3, Jay weighing 7 pounds

10 ounces (3,459 Gm.) and Larry 6 pounds 13 ounces (3,092 Gm.). They have since been followed and have progressed well without further vomiting. At this time, about three months after operation, Jay weighs 13 pounds 12 ounces (6,238 Gm.) and Larry 13 pounds (5,897 Gm.).

SUMMARY

A case of pyloric stenosis occurring in both infants of a set of monovular twins is reported.

Such a finding is evidence in favor of a genetic factor in the development of pyloric stenosis.

25 East Washington Street.

4753 Broadway.

OVARIAN CYST IN A PREMATURE INFANT

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AND
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More than 200 cases of ovarian tumors in infants and children were reviewed by Kennedy and Costin[1] and in about one third the growths were simple or multilocular cysts. Lanman[2] was able to find only 5 cases of ovarian tumors among 12,260 admissions to the surgical service of the Children's Hospital at Boston. While these tumors are rare in childhood, undoubtedly many of the cases are unreported. In addition to the case which we are reporting, one of us (G. Y. G.) has operated on a ruptured ovarian cyst with hemorrhage in a girl aged 10 years a granulosa cell tumor with precocious puberty in a girl of 8 years and 2 simple cysts in 12 year old girls, all unreported. Case reports of cystic and solid tumors in children under 1 year of age are very rare.

We found reports of sixteen cystic and two solid tumors of the ovary in infants under 1 year; eight of these tumors were operated on, five successfully and one unsuccessfully. The other nine tumors were found at autopsy.[3] In 8 of these patients, the ovarian growths were probably present before birth. Two of the infants were delivered with great difficulty because of the large size of their abdomen. In one of these infants the cyst burst during the delivery, causing death of the infant.

We have been unable to find any other report of a patient operated on as early as the one we are reporting. R. L. J. Kennedy, who recently reviewed the literature, was unable to find any reports of patients operated on so early.[2] In Dargeon's report of 14 patients with cysts in New York Hospitals,[3b] the youngest was 1 year old. Neikirk and Hudson,[3c] in 1948, reported a case almost identical to this one and reviewed the literature, finding only 1 other instance of a similar lesion.

With the recent trend toward specialization, infants are receiving more thorough examinations. This is responsible for the earlier discovery of these conditions in a stage at which an operation could be successful; this is better than waiting until the child's condition has deteriorated because of complications such as a twisted pedicle, loss of weight and cachexia so frequently associated with malignancy of a growth. With cooperation of the pediatrician, taking care of the nutrition, fluids and electrolyte balance—the anesthetic, either drop ether or 0.5 per cent procaine

1. Costin, M. E., Jr., and Kennedy, R. L. J.: Ovarian Tumors in Infants and in Children, Am. J. Dis. Child. **76**:127 (Aug.) 1948.

2. Personal communication to the authors.

3. (*a*) Lanman, T. H.: Ovarian Tumors in Childhood with Report of 5 Cases, New England J. Med. **201**:555 (Sept. 19) 1929. (*b*) Dargeon, H. W.: Ovarian Tumors in Childhood, Pediatrics **3**:773 (June) 1949. (*c*) Neikirk, W. I., and Hudson, H. W., Jr.: Giant Ovarian Cyst in Newborn Infant, New England J. Med. **239**:468 (Sept. 23) 1948. (*d*) Footnote 1. (*e*) Footnote 2.

hydrochloride solution being skilfully given—the surgeon can remove the growth as quickly as possible, using great care to handle the tissues gently and to minimize the loss of blood.

REPORT OF A CASE

B. K. S. was delivered Feb. 17, 1949. The labor was without incident until after the head was delivered. Considerable difficulty was encountered in delivery of the trunk of the baby. When this was finally accomplished, the abdomen was seen to be several centimeters larger than the head. The child weighed only 5 pounds (2,267 Gm.). It cried and reacted normally after delivery.

When the child was seen in consultation six hours after delivery, it seemed to be normal except for a very large abdomen; the enlargement was due to a cystic mass which extended from the symphysis pubis to a point between the umbilicus and xiphoid process. It was dull on percussion. Rectal examination revealed the mass high in the pelvis. The bladder was catheterized, but this caused no diminution in the size of the mass.

Roentgen examination of the abdomen, February 17, showed a uniform increase in density over a large area apparently due to a large dome-shaped mass that extended upward to the level of the eleventh thoracic vertebral body from either the lower abdominal or the pelvic area. The mass displaced the small intestines, stomach and colon upward and the descending colon laterally. The impression was that there was (1) a large distended urinary bladder and (2) a mesenteric cyst.

A roentgenogram of the abdomen after injection of opaque medium into the urinary bladder, February 17, showed the bladder to be normal in size and shape and without evidence of displacement. The uniform dome-shaped mass was again visualized as previously described. The impression was that there was a large cystic tumor-like mass, most likely a mesenteric cyst; however, a cystic tumor from the pelvic organs could not be ruled out.

A tentative diagnosis of mesenteric or urachal cyst was made. The baby's nutritional status was good and this status was maintained by clysis. During the day slight respiratory distress developed because of distention of the abdomen. On the second day of life, twenty-eight hours after delivery, using 0.5 per cent procaine hydrochloride solution and a minimal amount of drop ether the abdomen was explored through a left rectus incision. When the abdomen was opened a large bluish mass, measuring 9 by 12 cm. and 18 to 19 cm. in circumference, cystic in nature, presented itself in the wound. With minimal difficulty it was exteriorized. It was removed after the pedicle was ligated. The other ovary, the uterus and the tube appeared normal. The wound was closed with cotton.

REPORT OF PATHOLOGY

The specimen submitted consisted of a thin-walled cyst measuring 11.5 by 8 by 7 cm.; the total weight was 406 Gm. On the smooth surface, a very thin fallopian tube was seen. The wall of the cyst was paper thin and smooth on the interior. It contained 390 cc. of grossly bloody fluid.

MICROSCOPIC PATHOLOGY

Appended to the wall of the cyst, a small fallopian tube with delicate folds of mucous membrane was seen. There was fresh hemorrhage in the wall which had two distinct components. The thicker portion was made up of connective tissue with no distingushing features. In the wall, one small graafian follicle was seen. The epithelial lining consisted of a layer of granulosa type epithelium. This varied

considerably in thickness and in some places was up to three and four cells in depth. Because of the presence of bloody fluid in the interior and fresh hemorrhage in the wall, it was felt that torsion of the pedicle might have occurred prior to removal. There was no evidence of torsion of the cystic pedicle at the time of the operation. The bloody fluid was probably the result of trauma at the time of delivery.

Diagnosis.—A very large cyst of the ovary was diagnosed.

The convalescence was uneventful. About three weeks after the operation a small hard nodule was felt in the left inguinal canal. This could not be reduced, but it has not increased in size. The possibility that this could be a hernia of an ovary was considered, but it was decided to wait until the child is older before finding out the nature of the mass. The baby is now 4 months old, weighs 13 pounds (5,896 Gm.) and has apparently a normal growth and development pattern.

COMMENT

Difficulties in diagnosis of ovarian tumors in infants are due to the following causes: The conditions are not thought of because they are so rare. The uterus and ovaries are almost abdominal organs at this age; because they are more abdominal then pelvic they seldom give symptoms by pressure on the rectum or bladder. A differential diagnosis must be made from mesenteric, urachal and omental cysts, ascites, renal tumors, splenomegaly, hepatomegaly and solid mesenteric tumors. Because in so many of the ovarian tumors twisted pedicles developed the differentiation between them and appendical abscess is necessary. All babies with such tumors should be operated on as early as possible because of the danger of malignant change and complications such as a twisted pedicle with rupture and peritonitis which may cause a decline in the infant's ability to withstand operation.

SUMMARY

1. A case in which a premature infant less than 2 days old was successfully operated on for a follicular cyst of the ovary is reported. This is the earliest age that an infant with an ovarian cyst has been operated on successfully.

2. Dystocia was produced by the child's enlarged abdomen.

3. Infants in the first few days of life can stand an operation extraordinarily well, and they should be operated on as soon as the condition is discovered.

Abstracts from Current Literature

Metabolism; Infant Feeding; Milk and Other Foods

THE ENERGY EXPENDITURE OF BOYS AND GIRLS 9 TO 11 YEARS OF AGE (1) SITTING LISTENING TO THE RADIO (PHONOGRAPH), (2) SITTING SINGING, AND (3) STANDING SINGING. CLARA MAE TAYLOR, ORREA FLORENCE PYE, ANNE BARMAN CALDWELL and EDNA RUTH SOSTMAN, J. Nutrition **38**:1 (May 10) 1949.

Clara Mae Taylor and co-workers in these studies of energy expenditure found that boys spent more energy than girls when engaged in the same activity. The energy expenditure for standing singing for both girls and boys was only slightly above that for sitting singing. The energy expenditure for sitting singing of both boys and girls was above that of both for sitting listening to the radio, although the difference was very small in each case.

FREDEEN, Kansas City, Mo.

THE MICROBIOLOGICAL ASSAY OF "FOLIC ACID" AS APPLIED TO MILK. A. Z. HODSON, J. Nutrition **38**:25 (May 10) 1949.

A. Z. Hodson made a critical study of the assay methods for "folic acid" in milk. Data are presented which demonstrate that with present methods it is difficult to arrive at an accurate estimate of the average "folic acid" content of milk. However, the author reached the conclusion, in accordance with other investigators, that milk is a poor source of "folic acid."

FREDEEN, Kansas City, Mo.

RELATION OF IODINE TO THE GOITROGENIC PROPERTIES OF SOYBEANS. A. W. HALVERSON, MARIE ZEPPLIN and E. B. HART, J. Nutrition **38**:115 (June 10) 1949.

A. W. Halverson and others agree with H. S. Wilgus and co-workers that the slight goitrogenic property of raw and heated soybeans is not of practical importance in animal nutrition, since small amounts of iodine can effectively prevent the resulting thyroid enlargement. A ration containing 1 per cent of iodized salt (0.01 per cent potassium iodide) supplies a rat consuming 10 Gm. of ration a day with 7.6 microns of iodine, which is adequate to prevent goiter under all ordinary conditions.

FREDEEN, Kansas City, Mo.

THE BIOLOGICAL VALUE OF CORN AND WHEAT PROTEINS IN THE MALE INFANT, WITH A NOTE ON THE UTILIZATION OF *d*-TRYPTOPHAN. ANTHONY A. ALBANESE, SELMA E. SNYDERMAN, MARILYN LEIN, EMILIE M. SMETAK and BETTY VESTAL, J. Nutrition **38**:215 June 10) 1949.

A. A. Albanese and co-workers found that the nitrogen retention and weight gain of infants maintained on a synthetic diet, in which tryptophane-supplemented and lysine-supplemented commercial zein, constituted the principal source of nitrogen, were inferior, by reason of the poor digestibility of the zein, to those of infants on a casein diet with the same fluid, caloric distribution and nitrogen levels. A diet in which corn gluten reenforced with tryptophane and lysine provided the major source of protein also proved to be nutritionally inadequate for the infant. In contrast, a lysine-enriched wheat gluten diet supported a nutritional state in the infant comparable to that afforded by an evaporated milk formula. Inconclusive evidence is presented which suggests that the inclusion of *d*-tryptophane in the diet may have an untoward nutritional effect.

FREDEEN, Kansas City, Mo.

THE ESSENTIAL AMINO ACID CONTENT OF SEVERAL VEGETABLES. A. R. KEMMERER and R. ACOSTA, J. Nutrition **38**:527 (Aug. 10) 1949.

The protein of cauliflower as compared with whole egg protein is fairly well balanced in essential amino acids. It has optimum amounts definitely of methionine, valine, threonine,

histidine and tryptophane and possibly of arginine and phenylalanine. Sweet corn protein has approximately optimum amounts of histidine, leucine, phenylalanine and valine, and broccoli protein, of arginine and methionine. Carrots are deficient in all the essential amino acids.

FREDEEN, Kansas City, Mo.

A FAT EMULSION FOR INTRAVENOUS FEEDING. S. R. LERNER, I. L. CHAIKOFF and C. ENTENMAN, Proc. Soc. Exper. Biol. & Med. **70**:388 (March) 1949.

A fat emulsion of an olive oil (2 parts) dispersion stabilized by glycerin monostearate (1 part) was added to 5 per cent dextrose and prepared so that fatty acids were 10 per cent of the final product. Five dogs were given intravenous drips at the rate of 1 ml. a minute per kilogram body weight, receiving 16 to 31 daily injections. The fat was rapidly removed from the blood stream, and the fatty acid content of the liver was normal. No evidence of distress other than slight restlessness was observed during the injections.

HANSEN, Galveston, Texas.

RELATION OF FAT DEFICIENCY SYMPTOMS TO THE POLYUNSATURATED FATTY ACID CONTENT OF THE TISSUES OF THE MATURE RAT. V. H. BARKI, R. A. COLLINS, E. B. HART and C. A. ELVEHJEM, Proc. Soc. Exper. Biol. & Med. **71**:694 (Aug.) 1949.

Rats were first fed a fat free diet, at levels of 5 Gm. a day during a depletion period which caused severe emaciation, then nine of 39 rats were killed. The remaining animals were then allowed food ad libitum and 35 days later showed signs of fatty acid deficiency at which time 10 more were killed. After 71 days on the ad libitum regimen, most of the symptoms had disappeared and 10 more animals were killed. Two groups of 5 rats each were killed on the eighty-eighth day, the diet of one group of which had been supplemented with 2 drops (about 100 mg.) ethyl linoleate daily during the last 23 days. The tissues were analyzed by the spectrophotometric method for linoleic, linolenic and arachidonic acids in the body fat and the acids were found to vary with the symptoms—high at the end of the depletion period and low at the stage when fat deficiency symptoms were present. The higher levels of linoleic and linolenic acids at the time of recovery after a long period on the fat-free diet are considered evidence of synthesis of essential fatty acids in mature rats. Supplementation with ethyl linoleate increased the level of arachidonate in the body fat.

HANSEN, Galveston, Texas.

NUTRITIVE VALUE OF COOLED AND FROZEN MEATS. ENRIQUE D. U. PIERANGELI and BORIS ROTHMAN, Bol. Inst. internac. am. de protec. a la infancia **23**:170 (June) 1949.

Freezing produces physical changes, the extent of which are considerably reduced if a correct procedure of freezing is used.

Meat freezing produces minimal chemical changes.

The nutritive value of meat frozen under good conditions is the same as the nutritive value of fresh meat.

FROM THE AUTHORS' SUMMARY.

THE USE OF WHOLE MILK MADE ACID WITH LACTIC ACID. D. GOTTI, Clin. Pediat. **29**:472 (Aug.) 1947.

Beneficial results were obtained in the feeding of 37 young infants on formulas of dried homogenized lactic acid milk to which was added 2 per cent rice water and 5 per cent sugar. No gastrointestinal disturbances occurred; 90 per cent of the infants gained weight at a very satisfactory rate.

HIGGINS, Boston.

A POWDERED ACID WHOLE DRIED MILK WITH ADDED DEXTRINE AND MALTOSE IN THE FEEDING OF INFANTS. D. GOTTI, Clin. Pediat. **32**:1 (Jan.) 1950.

A proprietary dried whole lactic acid milk preparation (Pelargon Rosso Nestlé), containing added sucrose, starch and dextrine-maltose, proved a satisfactory food for normal, malnourished and sick infants.

HIGGINS, Boston.

THE USE OF CAROB FLOUR IN NUTRITIONAL DISEASES OF INFANTS. G. HALFER, Lattante **18**:415 (July) 1947.

Halfer is enthusiastic over the satisfactory results obtained in treating 36 infants with gastroenteritis by the use of feedings containing carob flour.

HIGGINS, Boston.

CHRONIC NUTRITIONAL DISEASE IN PERUGIA. P. LUCIANI, Lattante **18**:457 (Aug.) 1947.

A statistical study of the records of children under 3 years of age who were treated in the Pediatric Clinic at Perugia, Italy, since the beginning of World War II revealed that 15 per cent had a chronic nutritional disease. In 4 per cent of these the disease was due to constitutional factors, in 30 per cent to infections (mostly respiratory), in 60 per cent to improper feeding and in 6 per cent to uncertain causes. As many as 57 per cent of the cases referable to improper feeding were in breast-fed infants of undernourished mothers.

HIGGINS, Boston.

THE EFFECT ON RATS HELD ON A DEFICIENT DIET OF HUMAN MILK, EITHER FRESH OR AFTER STANDING. U. PELLEGRINI, Lattante **18**:527 (Sept.) 1947.

Observations were made on four groups of rats, one (group 1) on a normal diet and the other three on a rachitis-producing diet; one of the latter groups (group 2) acted as a control, and to the diet of the other two a supplement of human milk was added, to one (group 3) freshly expressed milk and to the other (group 4) day old milk.

Group 1 showed an average gain of weight of 57 Gm. in 40 days, group 2 a gain of 15 Gm., group 3 a gain of 24 Gm. and group 4 a gain of 21 Gm. Red and white blood cell counts and differential blood counts taken before and after the feeding experiments showed no significant differences.

Previously reported studies had shown that the breast milk in daily quantities up to 7 cc. afforded the rats no significant protection against the development of rickets.

HIGGINS, Boston.

PASSAGE OF METHYLATED PYRIMIDINE SULFAMIDES INTO HUMAN MILK. C. IMPERATO and L. LANDUCCI, Lattante **21**:162 (March) 1950.

The monomethyl and dimethyl sulfadiazine derivatives were found in the milk of mothers receiving those drugs and also in appreciable quantities in the blood of the nursing infants of these mothers.

HIGGINS, Boston

NUTRITIONAL DISTURBANCES IN CHILDREN: A STATISTICAL AND CLINICAL STUDY OF PROPHYLAXIS AND RECOVERY. A. BOLLETTINO, Lattante **21**:150 (July) 1950.

During the war years, the percentage of patients with diarrhea admitted to the pediatric clinic in Pavia showed a marked increase. The percentage has now fallen to the prewar level. However, the percentage of cures has risen from the prewar value of 57 per cent to the present value of 85 per cent.

HIGGINS, Boston.

STUDY OF KETONE BODY METABOLISM: EFFECT OF DIET ON THE ACETONE BODIES OF THE BLOOD FOLLOWING INTRAVENOUS INJECTION OF ACETONE. P. TOLENTINO and G. COTELLESSA, Minerva pediat. **1**:58 (Feb.) 1949.

Two diets of about 1,700 calories, one containing 142 Gm. of fat and 25 Gm. of carbohydrate and the other 9 Gm. of fat and 331 Gm. of carbohydrate, were used in this study on 5 children. Each child, after being on a diet for two days, was given intravenously 0.05 cc. of acetone per kilogram of body weight diluted in isotonic sodium chloride solution. Determinations of the acetone levels of the blood were made before and 5 minutes, 30 minutes, 4 hours and 12 hours after the injection. The data obtained were analyzed mathematically and the conclusion drawn that the high ketogenic diet caused ketolysis instead of being merely antiketogenic.

HIGGINS, Boston.

PROTEINEMIA AND LIVER TESTS IN THE MULTIPLE DEFICIENCY DYSTROPHIES OF THE NURSLING. OBDULIA JIMENEZ, JOSE DAL BORGO and RAUL ORTEGA, Rev. chilina de pediat. **20**:141 (April) 1949.

The authors studied proteinemia in infants with multiple deficiency manifestations, and their findings confirm the results obtained by Salleres. They also studied hepatic function in the same children, using cephalin-cholesterol flocculation, colloidal gold, thymol turbidity and tryptophanemia tests, which showed changes of different degrees according to the particular test and the stage of the condition.

Owing to the short observation period and the intensity of the humoral changes, depending especially on an insufficient supply of proteins, the findings must be considered preliminary, and only further studies will be able to determine whether there actually are hepatic functional alterations and whether these are transitory or definitive, apparent or true.

FROM THE AUTHORS' SUMMARY.

SOME ASPECTS OF ACUTE DISTURBANCES OF NUTRITION IN THE CHILD. JOSE LEGARRETA P., Rev. chilena de pediat. **20**:147 (April) 1949.

Five hundred and eighty clinical charts of children under 2 years of age admitted to the Calvo Mackenna Hospital with the diagnosis of acute nutritional disturbance are reviewed. The results obtained are analyzed statistically and expressed graphically.

These acute nutritional disturbances are more frequent in the spring, among infants artificially fed and in infants with chronic nutritional disturbances. It is interesting to note that there were very few premature infants among this clinical material.

No statistical evidence in favor of sulfonamide therapy could be obtained, since most of the children studied received this form of treatment.

The frequency with which intravenous administration of fluids, plasma therapy and blood transfusions were administered are commented on.

Forty-seven per cent of the infants admitted with a toxic syndrome died in the first 48 hours of hospitalization; this fact indicates the need of early treatment.

In the study of those infants with an acute nutritional disturbance plus a dysenteric syndrome it is interesting to remark on the frequency of the isolation of Escherichia coli and Bacillus proteus in the stool culture.

FROM THE AUTHOR'S SUMMARY.

HEMODILUTION AS AN ADJUVANT FACTOR IN THE DECREASE OF THE SERUM PROTEINS IN HUNGER EDEMA. HERMANN NIEMEYER, RAQUEL LOPEZ and JULIO MENEGHELLO, Rev. chilena de pediat. **20**:157 (April) 1949.

The authors present the results obtained in protein determinations made on the blood serum of children with chronic malnutrition. They point out the fact that the marked hypoproteinemia (about 4 Gm. per 100 cc.) that is systematically found during the edematous phase suddenly reaches normal values (about 6 per cent) when the edema disappears, generally between the tenth and the fifteenth day of treatment.

The general opinion is that the disappearance of the hunger edema is due to the increase in protein concentration, these proteins thus drawing the interstitial fluids to the vascular system. The authors believe that the reverse happens, i. e., that the disappearance of the edema increases the proteinemia, because this increase takes place in a period of one to three days, a fact that cannot be attributed to an increased production of proteins in the body. The authors' explanation presupposes a hydremic plethora that would dilute the proteins and other blood components. This situation would be conditioned by a renal insufficiency to eliminate water and salts due to circulatory disturbances that are present in these malnourished patients. The hunger edema would thus be produced by an overflow toward the interstitial tissues. In a supine position the renal circulation is improved, permitting the return to the normal plasma volume. In favor of this hypothesis, the authors advance their results of their own studies and investigations carried out by other authors on different aspects of the physiology of the malnourished person.

FROM THE AUTHORS' SUMMARY.

CLINICAL EXPERIENCE WITH STREPTOMYCIN-PRESERVED HUMAN MILK. FRIEDRICH LINNEWEH, Med. Klin. **44**:666 (May 27) 1949.

It could be shown that addition of streptomycin to fresh human milk in a concentration of 2 mg. per cent insures its preservation during the cold part of the year and prevents exogenous infection with Bacillus coli. In the amounts given no injury is to be expected in premature or newborn infants. It is to be noted that the p_H of preserved milk changes very little whether kept at 37 or at 20 C. for 100 hours, in comparison with that of untreated milk.

AMBERG, Rochester, Minn.

IODINE TREATMENT OF HYPOGALACTIA. W. BENOLIEL and A. MASI, Riv. di clin. pediat. **46**:766 (NOV.) 1948.

The authors treated with small doses of iodine, 6 drops of strong iodine solution U. S. P. (Lugol's solution) twice a day, 15 patients who, in the first five to six days after childbirth gave a quantity of milk greatly below average. In 10 of the 15 patients after six days of such treatment the milk secretion reached a quantity but little below normal.

At the same time, the authors determined on the same patients the measurement of basic metabolism, noticing in each patient an alteration—diminution or increase—of the thyroid function. After the iodine treatment the patients who had a marked increase in the milk secretion showed also a normalization in the function of the thyroid gland.

FROM THE AUTHORS' SUMMARY.

THE PRINCIPLE OF PROTEIN MILK AND OF LACTOSE. GÜNTHER MALYOT and IRMGARD DABLER, Med. Klin. **44**:982 (Aug. 5) 1949.

Ten infants 2½ to 10 months of age with dyspeptic symptoms were treated with protein milk until the symptoms had disappeared more or less. The milk contained 7 per cent carbohydrate in the form of a dextrin-maltose mixture (*Nährzucker*). This mixture was changed from one day to the next to beta lactose. It is known that alpha lactose hydrate under these conditions is injurious. The beta lactose was added immediately before drinking to avoid changes. No ill effects were noted, although the number of stools increased in some cases, particularly at the start. No ill effect on the fat digestion was noted. Sooner or later, rarely after more than 78 hours, a bifid flora replaced the mixed flora of the stools.

AMBERG, Rochester, Minn.

THE EFFECTS OF WAR DIETS ON THE CHILD. J. B. MAYER, Monatsschr. f. Kinderh. **97**:110, 1949.

Studies were undertaken to determine whether war diets (1939 to 1945) of German mothers would be reflected in the quality of their breast milk. It was found that there was no significant quantitative difference in the fat, carbohydrate and albumin content of breast milk of mothers with normal weight and those who were markedly underweight.

However, the author believes that the great increase of desquamative erythroderma (Leiner's disease) during these years speaks for qualitative changes in the constituents of breast milk. It is rare in countries with high nutrition standards, such as the United States. It was found in this survey that the disease, as usual, affected almost exclusively only breast-fed children and began during the first six weeks of life.

War diets had been one-fourth to one-seventh deficient in the required amounts of the essential amino acids.

Another proof of the decreased quality of breast milk was the increased incidence of rickets. There was also a higher number of rachitic children in the artificially fed groups.

Height and weight were found to be deficient especially among boys of 14 to 15 years and girls of 13 to 14 years. The average height deficiency was 2 per cent among all boys, 1.8 per cent among all girls; the average weight deficiency among boys was 9.4 per cent, among girls 11.2 per cent.

Undernourished children had lower blood pressure readings than children of normal weight. Other investigators report cardiac enlargement, tachycardia and higher incidence of enuresis among these children, but this was not confirmed by this study.

HARTENSTEIN, Chicago.

CALCIUM RESORPTION FROM THE RECTUM AND THE BLOOD CALCIUM LEVEL. HANS SAUTER, Schweiz. med. Wchnschr. **79**:221 (March 12) 1949.

It has been shown that at the end of pregnancy and during birth administration of calcium gluconate increases the tonus of the quiescent uterus; a dose of at least 0.8 Gm. given intravenously, intramuscularly or by rectum is needed. By means of hysterotonometry it could be shown that one of two unknown preparations contained calcium and approximately how much. The effect was produced without significant increase in the calcium level of the blood.

AMBERG, Rochester, Minn.

ALKALIPLASMA—TRANSFUSION. R. BUCHER, Schweiz. med. Wchnschr. **80**:522 (May 20) 1950.

A solution of 5 Gm. of sodium bicarbonate is prepared under proper precautions with 100 ml. of citrated blood plasma. On transfusion of such a solution the alkali reserve of the recipient's blood is maintained at a higher level for a longer time than on injection of the sodium bicarbonate solution alone.

AMBERG, Rochester, Minn.

MECHANISM AND REGULATION OF IRON RESORPTION. G. HEMMELER, Schweiz. med. Wchnschr. **80**:599 (June 10) 1950.

A specific diencephalic center is postulated for the regulation of the intermediary metabolism of iron.

AMBERG, Rochester, Minn.

DEVELOPMENT OF A NEW INFANT FOOD WITH LACTOBACILLUS BIFIDUS: I. THE BULGARIAN SOUR MILK (YOGHURT). J. B. MAYER, Ztschr. f. Kinderh. **65**:293, 1948.

The use in adult and infant nutrition of milk soured by Lactobacillus bulgaricus has been known to be beneficial for the treatment of enteric disturbances. Mayer obtained the cultures from Bulgaria and grew them most successfully on ewe's milk at 45 C. Although rate of growth and acid production could be influenced by different culture mediums, the species of bacteria was not changed. The ewe's milk culture was added to regular or skim sterilized cow's milk, and carbohydrate was added for infant feeding. The experimental study of the milk revealed that L. bulgaricus had bacteriostatic and bacteriocidal qualities. Acid is formed from milk sugar, but some partial decomposition of protein also takes place. Although the fat content and quality of the milk are unchanged by the bacterial action, its presence influences the growth of the bacteria.

Clinical observations were made on 32 infants, ranging in age from 3 weeks to 10 months, with intestinal disturbances. Skim milk or full sour milk (yoghurt) were used. The bacterial flora consisted almost entirely of L. bulgaricus after six to eight days, and clinically the infants improved rapidly. Similar results are not obtained with milk acidified by Streptococcus lactis, because this organism multiplies rapidly in the stools and has an irritative action on the bowels. Methods of culture and preparation of the milk are described in detail, and the results of chemical analyses are expressed in table and graph forms.

KURT GLASER, Chicago.

DEVELOPMENT OF A NEW INFANT FOOD WITH LACTOBACILLUS BIFIDUS: II. CULTURE OF LACTOBACILLUS BIFIDUS IN THE PRESENCE OF OXYGEN; III. BIFIDUS MILK; IV. STREPTOCOCCUS LACTIS-BIFIDUS MILK; V. LACTIC ACID-BIFIDUS MILK. J. B. MAYER, Ztschr. f. Kinderh. **65**:319, 1948.

Lactobacillus bifidus is generally considered an anaerobic organism. The author was able to culture it under oxygen in a sterile milk culture to which peptone, pepsin and a sterile aqueous yeast extract were added. He also described a culture plate on which he succeeded in culturing L. bifidus under aerobic conditions.

The plan of replacing pathogenic bacteria in the intestinal tract by harmless bacteria has been attempted by many investigators by the employment of bacteria foreign to the intestinal tract. Mayer, after succeeding in culturing L. bifidus under aerobic conditions, introduced the bacteria into cow's milk preparations for infant feeding. The bacteria occur physiologically in the intestinal tract of healthy breast-fed infants and grow best in the presence of lactose.

Regular cow's milk or skim milk may be used in the formula. The results with this food for healthy newborn infants, premature babies and infants with severe intestinal disturbances were excellent.

The use of bifidus milk had several disadvantages. Observations that infants fed successfully with buttermilk showed a bifidus flora in the intestines led to the investigation of factors stimulating the growth of L. bifidus. It was found that the Streptococcus lactis was such a factor and that with the presence of this coccus it was not necessary to sterilize the milk (overgrowth of the streptococcus at room temperature) and add pepsin, peptone and yeast extract. The regulation of the acidity still offered difficulties.

In order to overcome the variations in acidification due to Str. lactis, lactic acid was added; this at the same time inhibited the growth of pathogenic gram-negative bacteria and the Str. lactis and acted favorably on the growth of the bifidus bacteria. Clinical results with this milk form were very satisfactory.

KURT GLASER, Chicago.

ABSORPTION AND EXCRETION OF POTASSIUM. L. BARTA and L. BORSODI, Paediat. danub. **4**:190 (Oct.) 1948.

Potassium intake is followed by the retention of potassium. The absorption of potassium in the tubules generally increases and, therefore, less potassium is voided in the urine. The simultaneous administration of desoxycorticosterone acetate and potassium does not give rise to increased potassium excretion in healthy children. The authors believe that this phenomenon is due to the favorable action of desoxycorticosterone acetate on the carbohydrate metabolism. The increase of the reabsorption of potassium in the tubules after intake of glucose may be explained by the same approach.

This paper was already under print when Dicker's report showing similar results in rats was received. If the concentration of potassium in the glomerular filtrate increases, its tubular absorption, unlike that of the sodium and chloride ions, increases also.

FROM THE AUTHORS' SUMMARY.

ENDOGENOUS CREATININE CLEARANCE OF INFANTS SUFFERING FROM EXUDATIVE DIATHESIS. S. ZIMANYI, Paediat. danub. **4**:262 (Nov.) 1948.

In 12 children exhibiting skin phenomena due to the exudative diathesis the endogenous creatinine clearance was markedly decreased.

Exudative diathesis is not a pathological or clinical entity, and the endogenous creatinine clearance reveals only one part of the kidney function. With regard to the observations pointing to disorders of renal function in children suffering from exudative diathesis, it seems that examination of the tubular function should, in addition to the results referring to the decreased filtration, contribute to a better understanding of the concept of exudative diathesis. A knowledge of the clearance of the ions bearing on the fluid balance would also be of assistance.

FROM THE AUTHOR'S SUMMARY.

FRACTIONATED TEST MEAL IN NORMAL INFANTS. B. VOLTAY, Pædiat. danub. **4**:208 (Oct.) 1948.

Ten male and 10 female infants between 2 weeks and 6 months, all fed on mother's milk, were given 0.10 Gm. caffeine dissolved in 150 ml. of water on an empty stomach. Five milliliters of the gastric contents were then withdrawn every 10 minutes and the samples examined for free hydrochloric acid and total acidity. No free acid was found under 20 minutes after the test meal, then there was an increase for 10 minutes; during the next 10 minutes the acidity began to decrease, and at 40 to 50 minutes the stomach was empty. When the data are compared with those recorded for adults, it seems that with age gastric acidity increases while the evacuation time decreases.

FROM THE AUTHOR'S SUMMARY.

FRACTIONAL TEST MEAL IN INFANTS WITH TOXICOSIS AND DYSTROPHY. B. VOLTAY and E. TOMORY, Paediat. danub. **4**:268 (Nov.) 1948.

Twenty-four infants with grave toxicosis were examined with a test meal consisting of 0.10 Gm. of caffeine dissolved in 150 ml. of distilled water. Most of the infants showed low or normal values; there were only a few who showed hyperacidity. The fluid ingested was

evacuated by the stomach within 50 minutes at the most. The observations did not support the current opinion that gastric acidity is always increased in acidotic states. The cause of the low acidity values is unknown, but they might be ascribed to the changes in the plasma bicarbonate level, which is always decreased in acidotic states.

The acidity values found for 12 infants with atrophy roughly corresponded to those observed for normal infants, with the exception of three infants with practically no hydrochloric acid and two others showing moderately increased acidity.

Eight infants with dystrophy were also tested, and they all showed high values. This was especially striking in cases in which loss of appetite was present.

From the Authors' Summary.

Vitamins; Avitaminoses

Explanation of Rickets in the Light of More Recent Knowledge. E. Rominger, Lattante **20**:200 (April) 1949.

This essay reviews the recent chemical investigations as to the cause of rickets. Special attention is given to the role of sodium citrate as an adjunct to vitamin D in preventing rickets.

Higgins, Boston.

Antirachitic Prophylaxis with Vitamin D_2. J. Marinoni, Lattante **20**:275 (May) 1949.

In the years 1944 to 1947 at Padua, Italy, 61 infants were given 300 international units of vitamin D_2 (irradiated ergosterol) daily over the four month winter period; another group (25 infants) received two single doses of 600,000 units at eight week intervals. Of the first group, 16 (26 per cent) showed signs of rickets, confirmed by blood chemical studies, and 1 (8 per cent), latent tetany at the end of the eight weeks. Of the second group, only 2 (8 per cent) showed signs of rickets and none showed signs of tetany. The percentage of patients in these groups showing rickets has been gradually decreasing in the postwar years.

Higgins, Boston

Absorption of Vitamins. Alvaro Masi, Riv. clin. pediat. **48**:160 (March) 1950.

Masi cites the blood levels he obtained in children after an intramuscular injection of vitamin A and a dose of vitamin A in an oily solution given by mouth. In the second part of his work he also refers to the amounts of vitamin A contained in the liver of guinea pigs treated with the same vitamin A preparation by mouth and through intramuscular injections.

He discusses the particulars of the absorption of vitamin A in an oily solution injected in the muscles.

From the Author's Summary.

Preliminary Report on the Action of the Vitamin T Complex in the Treatment of Disturbances of Growth in Infancy (Dystrophies, Atrophies). G. Nussbaumer, Med. Klin. **44**:636 (May 20) 1949.

Vitamin T complex has been obtained by Goetsch from the yeast Torula utilis as torutilin. Infants aged 11 weeks to 7 months and a 3 year old girl in severe states of malnutrition were treated with torutilin, which was given in a dosage of two times 5 drops to two times 10 drops, occasionally three times 10 drops, by mouth. With the last dosage the motor unrest increased to such an extent that sedatives were required. The 3 year old girl had a celiac disease. A large number of infants in the hospital responded to torutilin with prompt increase of body weight and improvement of the blood. This improvement could be maintained for weeks, but then the increase in weight diminished and finally the infants no longer reacted to torutilin.

Amberg, Rochester.

Shock Therapy of Rickets with Vigantol in Powder Form. Doris Wendt, Med. Klin. **44**:1121 (Sept. 2) 1949.

The vigantol powder (Merck) used contains 15 mg. of vitamin D_2 in 5 Gm. of powder. It was given in this amount to a number of rachitic infants, with beneficial results.

Amberg, Rochester.

TREATMENT OF RICKETS WITH VIGANTOL "FORTE" POWDER. OTTO CAMMANN, Med. Klin. **44**:1159 (Sept. 9) 1949.

Vigantol "forte" powder contains 15 mg. of vitamin D_3 in 1.5 Gm. of a calcium salt-glucose mixture. It can be easily given by mouth after it has been taken up in about 20 ml. of fluid. Its therapeutic value proved equal to that of the vitamin D_3 in oil, but it has some practical advantages. It seems it can be given to the dyspeptic infant in a fat-free medium.

AMBERG, Rochester.

CLINICAL AND HUMORAL STUDIES WITH IMPLANTS OF CALCIFEROL (D_3). BESANCON, L. JUSTIN, and H. P. KLOTZ, Schweiz. med. **79**:914 (Sept. 24) 1949.

Implantations of 75 to 100 mg. of compressed calciferol in patients with tetany produces an important increase of calcium in the blood, lasting four to five weeks, and it is accompanied with a slight elevation of the blood phosphorus and a decrease of phosphaturia. In dogs deprived of the parathyroid glands the blood calcium also increases on implantation of calciferol. Estradiol benzoate administered to patients opposes the effects of calciferol implants.

AMBERG, Rochester.

Hygiene; Growth and Nutrition; Public Health

FIELD RECORDS IN MATERNAL AND CHILD HEALTH WORK. S. V. RAJA RAO, Indian J. Pediat. **17**:1 (Jan.) 1950.

Public health efforts in the rural areas are described briefly. Less than half the mothers are delivered by midwives, the rest by untrained persons. Postpartum visits average three in ten days. Maternal mortality varied from 3.3 to 7.76 per cent over twelve years, which is considered good as compared with 50.9 per cent in the hilly areas of the state. The infant mortality rate was 130 in 1948. Seventy-five per cent of infant deaths occur before 1 month. The infant mortality rate was 154 when delivery was by untrained persons, owing largely to sepsis of the cord, sepsis from branding the child after delivery and generally poor socioeconomic conditions. Thirty-five per cent of the infant deaths were due to prematurity.

MCGUIGAN, Evanston, Ill.

THE ORIGIN AND RESULTS AT THE PROVINCIAL INSTITUTE FOR CHILDREN IN SASSARI IN THE YEARS 1942-1948. G. A. PIANA, Ann. ital di pediat. **2**:359 (Aug.) 1949.

Piana examines the conditions of organization and working of the Provincial Institute for Children of Sassari whose management he held from 1942 to 1948.

He examines also the causes of increased mortality in the years of that period and suggests a better, more complete and more proper organization in a new settlement of the Institute in the near future.

FROM THE AUTHOR'S SUMMARY.

SCOPE AND GOALS OF THE MATERNAL AND CHILD DIVISION OF A HEALTH CENTER. JULIO C. CHENU-BORDON, Bol. Inst. internac. am. de protec. a la infancia **22**:20 (March) 1949.

According to the author, the protection of childhood has its origins in the recognition of children's rights; and the state and the community must assure the benefits of these rights for each child from the beginning of pregnancy until the time of majority, when he takes his own individual place in society.

Health centers must have, first of all, an antepartum service with clinics that may carry their influence and attention to the home of the expectant mothers; later there must be an ample child health service, with preschool and school hygiene clinics and pediatric, dietetic and vaccination clinics.

Preschool hygiene clinics would take care of healthy children from birth to 7 years; school hygiene clinics would take care of children going to school and watch over the health of teachers and principals, and pediatric outpatient clinics would serve two groups of sick children; one for children under 2 years and the other for children from 2 to 16 years of age.

FROM THE AUTHOR'S SUMMARY.

MORBIDITY IN CHILDREN OF SCHOOL AGE IN SOUTHERN ITALY IN THE POSTWAR YEARS. L. AURICCHIO, Pediatria **57**:289 (May) 1949.

Infectious diseases, especially tuberculosis, reached a high peak in 1946 among children in Southern Italy; virus diseases were very frequent and served as a precursor of acute respiratory tract infections. The wretched conditions to which the population of the war-devastated areas return present great obstacles to good hygiene for children and to prevention of the spread of tuberculosis.

HIGGINS, Boston.

WEIGHT AND HEIGHT IN OUR NEWBORN AND INFANTS TO ONE YEAR OF AGE. ALFREDO U. RAMON GUERRA, Arch. de pediat. d. Uruguay **21**:81 (Feb.) 1950.

The weight of newborn babies from a high social-economic level is 3,560 Gm. for the boys and 3,405 Gm. for the girls, a difference statistically significant. When these results are compared with those of E. Peluffo, a significant difference is obtained. The standard deviation and the coefficient of variation were also studied. Some of the methods are indicated. The distribution of incidence was analyzed in relation to the normal curve of Gauss. The average height of the boys was 51.5 cm. and that of the girls 50.1 cm. Afterward the average results are applied to the Wetzel grid; the result shows a physical constitution within the middle channel and a chronologic level of development (auxodrome) which differs little from the median types found in other countries for the same age group.

FROM THE AUTHOR'S SUMMARY.

CHILD CARE IN RURAL DISTRICTS. ALESSAŃDRO LAURINSICH, Paediat. danub. **5**:1 (Jan.) 1949.

The difference in the care of infants in towns and villages is due to several factors. Social diseases, especially syphilis, are less frequent in the country, and village mothers are more willing to insist on breast feeding than mothers in town. On the other hand, housing conditions are worse in the country, and, since the population is conservative, it is difficult to propagate modern and rational principles. The level of child education runs parallel with the intensity of agriculture. Small estates and intensive agriculture favor the spread of right principles, while large estates and extensive agriculture are connected with housing shortage and low hygienic conditions.

By raising the standard of life, infant mortality can be reduced, although living conditions exert only an indirect influence on mortality. Pediatric centers are likely to combat ignorance; hence the control of infants and children by nurses and pediatricians should be introduced. To this end, advisory centers should be erected.

Infant care is to be started during pregnancy. Care during pregnancy should be the duty of the obstetrician and midwife operating at labor. District obstetrical homes cannot for the time being be created for economic reasons; their full utilization cannot be secured and this constant staff would represent a great burden to the community. The problem could be solved by education of assistant midwives to be called for only in case of necessity.

As more and more women are taking work in the country, artificial feeding is spreading. There is no measure to combat this process, as mothers in villages cannot be supported to such an extent as in towns. Nursing mothers should be supported by the state during the lactation period.

Infant and child protection is to be completed by district clinics, and all rural hospitals should be compelled to equip a pediatric department.

FROM THE AUTHOR'S SUMMARY.

THE METHOD OF ESTIMATION OF VALUES OF NORMAL AND PATHOLOGICAL GROWTH IN CHIDLREN AND YOUTHS. G. DE TONI, Bull. d. schweiz. Akad. d. med. Wissensch. **6**:212 (March) 1950.

De Toni makes a brief analysis of growth considered as a biologic phenomenon. After outlining the relation existing between somatic growth and mental development, he discusses the evaluation of the successive stages of physical development. Various authors have chosen different factors as criteria, e. g., the relation between height and weight, muscular subcutaneous and skeletal development, variations in vital capacity, etc.

In this field, repeated measurements on numerous groups of persons of the same age are less informative than periodic measurements on the same subject.

The system of periodic measurements on the same subject, which is at present in use in several centers where growth is being studied, particularly in America, is of great interest.

In daily clinical practice, however, it is necessary to adopt a method which is easily accessible not only to those of the medical profession but also to those of the teaching profession and the parents and which gives at least an indication of the nature of the somatic development.

De Toni considers that this result can easily be obtained simply by measuring the weight and the height and calculating the relative deviation with respect to normal values for the age considered. On the basis of these data, he proposes a new auxological classification, thanks to which it is possible to group easily the irregularities and deviations of physical growth and to represent them graphically in a clear and stimulating manner.

FROM THE AUTHOR'S SUMMARY.

Prematurity and Congenital Deformities

GARGOYLISM (LIPOCHONDRODYSTROPHY). GEORGE A. JERVIS, Arch. Neurol & Psychiat. **63**:681 (May) 1950.

The author presents a series of 10 cases, of which three show the complete clinical picture and seven lack various characteristic findings. Diagnostic criteria for recognizing these cases are reviewed. Etiology is discussed, and a table is included which lists all the cases reported in the literature. The disease is shown to be genetically determined, apparently by a single recessive gene.

McGUIGAN, Evanston, Ill.

THE PREMATURE INFANT. I. P. JAFFE, South African M. J. **24**:358 (May 13) 1950.

The author offers a new concept in the care of premature infants; it appears to consist mainly of preliminary starvation for 72 hours.

McGUIGAN, Evanston, Ill.

A CLINICAL STUDY OF A CASE OF BILATERAL CONGENITAL ANOPHTHALMIA WITH A MEGACRANIA AND PROFOUND MENTAL DEFICIENCY. M. SCHACHTER, Ann. pædiat. **174**:393 (June) 1950.

This is a clinical description of a case of bilateral congenital anophthalmia in a girl aged 4 years 10 months, in whom there was, in addition, megacephalus and severe mental retardation. With regard to the etiology, it appears that syphilis and alcoholism of the parents can be excluded. It was impossible to prove that some toxic damage occurred to the fetus, e. g., rubeola or toxoplasmosis. It is reported, however, as an exceptional occurrence, that during the fifth month of pregnancy the mother was buried under some debris during an aerial bombardment.

The pathology of ocular malformations in general and of anophthalmia in particular is discussed.

FROM THE AUTHOR'S SUMMARY.

Newborn

EXTRINSIC DUODENAL OBSTRUCTION IN THE NEWBORN. ALLAN E. SACHS, Ann. Surg. **131**:117 (Jan.) 1950.

Abdominal surgery in the newborn infant is concerned mainly with the correction of congenital malformations and defects. An intimate knowledge of the exact nature of the anatomic disturbance is the all-important factor in saving lives.

One is impressed by the ease with which the conditions can be corrected if the anatomic defects are recognized. The dissection is delicate, but no difficult anastomoses are required.

According to Sachs, abdominal surgery in the premature and newborn infant can safely be done with open drop ether anesthesia if oxygenation is aided by an oxygen catheter placed under the ether mask.

Three cases are reported.

BANTIN, Omaha.

THE INCIDENCE OF MONGOLOID IMBECILITY IN THE NEWBORN INFANT. GEORGE F. PARKER, J. Pediat. **36**:493 (April) 1950.

Among 27,931 live born infants there were 32 with mongolism, an incidence of 1.15 per 1,000. Race and sex differences were not significant. There was, however, a greater frequency among premature infants.

MACDONALD, Pittsburgh.

PROTHROMBIN DEFICIENCY OF THE NEWBORN. ALEXANDER RANDALL, IV and J. PERLINGIERO RANDALL, Proc. Soc. Exper. Biol. & Med. **70**:215 (Feb.) 1949.

To the serum or plasma of 12 full term infants less than 5 days of age in whom the plasma prothrombin time was prolonged, were added (1) plasma from 12 normal adults, (2) plasma from six normal infants with normal prothrombin times yet who had not been given vitamin K, (3) plasma from five adults who had received dicumarol® for thrombotic disease but were otherwise healthy and (4) plasma from two adults with liver disease. The prothrombin time of the various plasmas and plasma mixtures was determined by the Quick method, and the average of at least three determinations was noted. When these infants' plasma was mixed with small amounts of normal adult plasma the prothrombin time was shortened, and when it was mixed with the normal infants' serum a similar though less marked shortening occurred. Only a slight shortening occurred by the addition of plasma from "dicumarolized" adults and patients with liver disease. From these studies the authors believe that the prolonged prothrombin time in newborn infants, studied by the one stage technic, cannot be explained by a simple deficiency of prothrombin but rather by a factor which accelerates the conversion of prothrombin to thrombin.

HANSEN, Galveston, Tex.

THE INCIDENCE OF RH-NEGATIVE PERSONS AND OF HEMOLYTIC DISEASE OF THE NEWBORN IN THE PROVINCE OF BOLOGNA. B. RONDININI and E. NEROZZI, Clin. pediat. **32**:25 (Jan.) 1950.

Of 303 adults tested at the clinics of the University of Bologna, 12.6 per cent were found to be Rh negative. This figure is lower than the percentage reported for Italy as a whole (16.5 per cent). Statistically, the chance of an Rh-positive father and an Rh-negative mother is 5.4 per cent. There has been an average of only two cases of hemolytic disease of the newborn per 1,000 deliveries in the obstetric clinic of the University of Bologna.

HIGGINS, Boston.

TREATMENT OF ERYTHROBLASTOSIS FETALIS BY EXCHANGE TRANSFUSION. M. MITERA, V. KAFKA and J. SEDLAK, Ann. paediat. **172**:155 (March) 1949.

On the basis of their experience with 9 newborn infants with icterus gravis neonatorum whom they treated by exchange transfusions, the authors came to the following conclusions:

1. Exchange transfusion is justified in cases in which the past history and serological findings are in favor of erythroblastosis, even if the clinical picture is not fully developed in the newborn. Positive serologic findings are (*a*) incompatibility of baby's and mother's Rh system and (*b*) signs of isoimmunization, i. e., Rh antibodies in mother's and baby's serum.

2. The cooperation among the children's specialist, surgeon, obstetrician, gynecologist and serologist is essential for the exchange at the earliest possible moment. The sooner operation is done, the smaller is the damage caused to the organism by Rh isoimmunization and the better are the results. Therefore, it is essential to know the mother's serologic reactions during pregnancy and, if necessary, advise a premature delivery.

3. The authors injected the citrated blood into the cubital or saphenous vein and withdrew the blood from the radial artery. They recommend the injection of an amount of blood equaling two tenths of the baby's weight and the withdrawal of about 80 cc. less.

FROM THE AUTHORS' SUMMARY.

CLINICAL AND SEROLOGIC PROBLEMS OF THE RH BLOOD GROUPS. PETER DAHR, Schweiz. med. Wchnschr. **79**:1047 (Nov. 5) 1949.

Dahr recommended previously a provocation of Rh antibodies with intravenous injections of small amounts of citrated whole blood from the husband. Now injection with washed erythrocytes is preferred to whole blood, obviating the necessity of testing for A, B and O blood group incompatibility.

After the injection of an equivalent of 3 cc. whole blood, the blood is examined daily for Rh antibodies. When the results of the examinations are negative, another injection corresponding to 5 cc. whole blood is given. If in the following six days no Rh antibodies including blocking antibodies are demonstrable, it can be assumed that erythroblastosis due to Rh factors need not be considered. If during a new pregnancy antibodies should be produced, it may be of prognostic significance. The peculiarity that Rh-conditioned transfusion accidents occur relatively late, usually an hour after the end of the transfusion, is discussed. The existence of hitherto unknown Rh anibodies is assumed. It is recommended that the blood of an expectant mother be tested early during recognized or suspected pregnancy with citrated blood as used in the provocation above described, that is, 3 or 5 cc. citrated blood of a healthy Rh-positive blood group O person who will be available for desensitization. During pregnancy injections of washed red corpuscles from this person are to be given frequently in amounts to be determined by further work. It is expected that the continuous presence of Rh corpuscles in the blood will depress formation of Rh antibodies. This proposal could not yet be tested.

In the concluding part of the paper allergic factors, i. e., Rh factors, are considered. Such factors are not regarded as of importance in the formation of moles, and it does not seem that vitamin E deficiency plays a role. The pathogenesis receives attention, and the various factors are discussed further. Dahr's own material comprises 606 cases of abortion. Of these, 10.6 per cent were of unknown etiology. Mole formation constituted 31.4 per cent of all abortions and 52.8 per cent of the spontaneous abortions.

AMBERG, Rochester, Minn.

Acute Contagious Diseases

PENICILLIN IN THE TREATMENT OF DIPHTHERIA. HENRY B. BRUYN, HENRY BRAINERD and BRUCE W. LEPPLA, Am. J. M. Sc. **219**:408 (April) 1950.

One hundred and forty-seven patients with diphtheria, treated with either antitoxin alone or antitoxin and penicillin, have been studied.

Penicillin therapy in addition to the antitoxin did not affect the incidence of complications or the mortality in these patients.

In the patients treated with penicillin in addition to antitoxin the diphtheria organisms showed a tendency to disappear from the nose or throat culture slightly earlier than in the patients receiving antitoxin alone.

These results are similar to those of many of the reported investigations on the use of penicillin in diphtheria.

HENSKE, Omaha.

ANOXIC ENCEPHALOPATHY FOLLOWING POLIOMYELITIS. T. THEODORE STEEGMANN and HERBERT V. DAVIS, Arch. Neurol. & Psychiat. **63**:774 (May) 1950.

Evidence of cortical injury developed in a 10 year old poliomyelitis patient after a period of anoxia. Death occurred three months later. Pathological studies showed the typical changes of poliomyelitis, with extensive degenerative cortical encephalopathy. These cortical changes did not resemble poliomyelitic damage but were the same as those observed in other types of anoxia encephalopathy.

MCGUIGAN, Evanston, Ill.

AUREOMYCIN TREATMENT OF PERTUSSIS. SHIH-MAN CHANG, EDWARD WELLS and EDWIN PLACE, J. Pediat. **36**:443 (April) 1950.

Aureomycin produced significant bacteriologic and clinical improvement in 17 of 22 patients with pertussis. The authors suggest a dose of 60 mg. per kilogram a day. Treatment should be continued for 10 days.

MACDONALD, Pittsburgh.

ELECTROENCEPHALOGRAPHIC FINDINGS IN MEASLES ENCEPHALITIS. HORACE L. HODES and SAMUEL LIVINGSTON, J. Pediat. **36**:577 (May) 1950.

Hodes and Livingston found normal electroencephalograms in children with uncomplicated measles. Eight children with measles encephalitis showed similar electroencephalographic changes consisting of abnormally slow high voltage waves. Seven of these patients recovered completely although the electroencephalograms returned to normal some time after the patients appeared to have recovered. In one case the electroencephalogram did not return to normal, the patient's clinical condition did not improve and death resulted.

MACDONALD, Pittsburgh.

THE USE OF PERTUSSIS AGGLUTINOGEN SKIN TEST DURING ACTIVE INFECTION WITH WHOOPING COUGH. JEROME L. KOHN, L. WANNAMAKER, S. KAPLAN and K. SHEPARD, J. Pediat. **36**:614 (May) 1950.

The authors tested 292 children ill with pertussis. The results were equivocal. This test is not an accurate index of immunity following an infection with pertussis.

MACDONALD, Pittsburgh.

CLINICAL CONCEPT OF POLIOMYELITIS. EDWARD B. SHAW and HULDA E. THELANDER, Pediatrics **4**:277 (Sept.) 1949.

This study is based on about 1,000 cases of poliomyelitis. Clinical studies concern the only animal spontaneously affected. Epidemic spread, whether due to contact or due to fecal contamination, may result in latent infection converted into inflammatory disease by numerous precipitating traumatic factors.

Initial temperature rise in the biphasic course is not proved to be due to poliomyelitis virus and may be due to other infection which acts as a precipitating cause.

The sequelae of weakness, muscle spasm, pain, muscle atrophy and vasomotor changes are not necessarily interrelated and may occur fairly independently. Muscle weakness is segmental and not symmetric. Some degree of weakness usually occurs in patients in whom the diagnosis is established with certainty and is often overlooked if the trunk is involved. Muscle spasm reaches its height later than weakness and is more symmetric, and the late oncoming stiffness helps to differentiate poliomyelitis from other causes of meningeal irritation.

Treatment is symptomatic and is directed especially toward preservation of normal muscle length; there are support against overstretching and gentle stretching against contracture. Heat in any form is useful for relief of pain and muscle spasm. Special complications require carefully designed treatment. Of greatest importance is the avoidance of anoxia.

Late care continues the preservation of normal muscle length and gradual reeducation of integrated muscle function. All methods of treatment, including the use of braces and splints and the late surgical correction of deformities, should be individualized to suit the particular patient.

Some one physician should direct each patient so as to integrate the different medical skills necessary for total care and to guide the patient in his own efforts toward recovery.

FROM THE AUTHORS' SUMMARY.

MEASLES ENCEPHALITIS: CLINICAL AND ELECTROENCEPHALOGRAPHIC STUDY. MELCHIJAH SPRAGINS, BURTON M. SHINNERS and BETSEY ROCHESTER, Pediatrics **5**:599 (April) 1950.

The acute symptoms of the onset of 31 cases of rubella complicated by encephalitis are presented. The correlation of the incidence of severe residua with slow recovery from acute symptoms is pointed out.

The residual symptoms developing in 12 patients followed over a period of two years are described. It is emphasized that disturbance of personality, concentration and memory are most frequent in occurrence. The electroencephalographic changes occurring in these patients are described, and a correlation between the clinical severity of residua and electroencephalographic changes is presented.

The need for close follow-up of the convalescing postencephalitic patient is stressed so that developing behavior difficulties may be recognized and intelligently managed. The value of the electroencephalogram in the evaluation of the difficulties of the postencephalitic patient is discussed.

Selected reports of cases are presented demonstrating the electroencephalographic changes and the associated clinical manifestations.

FROM THE AUTHORS' SUMMARY.

DIAGNOSIS AND TREATMENT OF POLIOMYELITIS IN THE ACUTE STAGE. SEYMOUR HEYMANN, South African M. J. **24**:373 (May 20) 1950.

The salient diagnostic points in various forms of poliomyelitis are discussed and the modern treatment outlined.

McGUIGAN, Evanston, Ill.

POLIOMYELITIS: POSTPARALYTIC TREATMENT—ORTHOPAEDIC ASPECT. HAMILTON BELL, South African M. J. **24**:379 (May 20) 1950.

Orthopedic treatment of poliomyelitis is discussed in detail. Methods of preventing contractures during the acute stage are presented briefly, with fairly detailed discussions of appliances, operations, manipulations and operations applicable after the acute stage is passed. Means of controlling growth in extremities are listed, and various bone operations for correction of deformities are described.

McGUIGAN, Evanston, Ill.

STREPTOMYCIN THERAPY IN WHOOPING COUGH PNEUMONIA. P. KISS, Ann. pædiat. **174**:209 (April) 1950.

Three cases of patients with whooping cough associated with grave pulmonary alterations are reported. The patients were 7, 3 and 3 years old, respectively. The pulmonary changes observed were purulent bronchitis, confluent bronchopneumonia in several lobes, microfocal bronchopneumonia, peribronchitis demonstrable beyond any doubt, interstitial infiltrations, emphysematous foci, swollen lymph nodes and interlobar and parietal pleurisy.

The changes proved resistant to the usual therapy. In one of the cases it was tried to influence the process by penicillin, high intravenous doses of vitamins C and K and vitamin C by mouth. Instead of improvement aggravation was noted. Therapy completed with streptomycin had a dramatic effect in two patients, while in the third patient improvement of the general condition and normal temperature came only gradually.

In one of the patients severe anemia and heart lesions complicated the third week of whooping cough. In this patient, therapy was completed by strophanthin and transfusions of blood.

The lung changes were serially controlled by roentgenography. In this manner the improvement could be observed. Although the pulmonary changes showed improvement on roentgenography, the coughing attacks did not cease. In one of the patients the attacks recurred at a time when both the general condition and the roentgenogram pointed to a marked improvement of the disease.

We share the opinion that pulmonary alterations occurring during or after the third week of whooping cough are partly due to Hemophilus pertussis and partly to various other infectious agents. Considering this, one must not be satisfied with the administration of streptomycin alone, but there should be given combined therapy with streptomycin and penicillin completed by high doses of vitamins C, K and B_1 both orally and intravenously. On the other hand, the third patient yielded conclusive evidence for the assumption that penicillin and vitamins C and K alone do not suffice for recovery.

As for the time when the combined therapy should be initiated, I believe that it should be introduced when, together with fever, clinical and roentgen examination show the presence of anatomic changes in the lungs or when purulent bronchitis has joined a "pure case of pertussis." This way therapy will combat both the vital danger and the conditions giving rise to consecutive bronchiectasis.

As to the duration of the combined streptomycin therapy, I suppose that penicillin and vitamin K can be safely omitted when the bubbling rales, fever and symptoms of purulent bronchitis (purulent sputum) have ceased for more than 48 hours. On the other hand, the

administration of streptomycin and vitamins C and B_1 should be continued until the roentgen examination shows that the process has completely receded. However, one need not await the cessation of the cough, which may last for several weeks.

As it is known that whooping cough is liable to recur, patients should be followed up for a long time after recovery. As to the dosage of streptomycin, 1.0 Gm. was given intramuscularly on the first day divided into eight doses, and subsequently the dose was reduced daily by 0.1 Gm. If rapid improvement occurred, the dose was decreased to 0.5 Gm. as early as on the fourth or fifth day. This amount was also administered in eight equal parts every three hours. We believe that in small children if a protracted treatment is given the dose may further be reduced to 0.3 Gm. a day.

The cases strengthen the assumption that even the severest pulmonary complications of whooping cough can be favorably influenced by a combined streptomycin therapy.

FROM THE AUTHOR'S SUMMARY.

WATERHOUSE-FRIDERICHSEN SYNDROME. NINO FRONGIA, Ann. ital. di pediat. **3**:27 (Feb.) 1950.

On the basis of a personally observed case, Frongia reviews the literature of the Waterhouse-Friderichsen syndrome and in particular the etiology and pathogenesis of this disease.

If meningococcus is the most frequent determining agent, cetrainly it is not the only germ capable of determining this disease, which may have many pathogenic factors, among which the author gives particular importance to the thymolymphatic constitution.

FROM THE AUTHOR'S SUMMARY.

TREATMENT OF WHOOPING COUGH WITH VITAMIN C. J. C. DE WIT, Maandschr. v. kindergeneesk. **17**:367, 1950.

DeWit describes 90 children suffering from whooping cough who were treated with ascorbic acid by injection and by mouth within a period of 2 years. The dose amounted to 500 mg. a day for seven days, after which it was reduced by 100 mg. every two days, ending with 100 mg. a day till clinical cure was obtained. The average duration of illness amounted to 15 days in children treated by injections and to 20 days in children treated by mouth.

The average duration of illness of 20 children treated within the same period with vaccines amounted to 34 days.

Ascorbic acid given in the catarrhal stage of the illness prevented the convulsive stage in 75 per cent of the children whereas the number of complications was negligible. The ascorbic acid excretion curves in the urine showed that the excretion was far less than the absorption, and the increase in excretion corresponded to the clinical recovery.

Absorption and excretion of ascorbic acid became equal three days after clinical cure, which indicates that it would be wise to prolong the treatment for about that time after apparent clinical recovery.

FROM THE AUTHOR'S SUMMARY.

EXPERIENCES WITH PERTUSSIS SERUM FOR HYPERIMMUNITY. F. A. WILLEMIJNS, Maandschr. v. kindergeneesk. **17**:374, 1950.

A small quantity of pertussis serum for hyperimmunity was prepared after repeated injections of pertussis vaccine for hyperimmunity in high dosage in 100 adults. Titration of the agglutinins in the serum was the method used to estimate its activity. One hundred and fifty children with pertussis were treated with this serum.

The results obtained in 101 children were analyzed with regard to age, duration of the diseases before the injections of serum and severity of the case. Most of the children were given three intramuscular injections of 20 ml. serum. Penicillin and/or sulfonamides was given in addition in 31 cases.

Of the 51 children with complicated pertussis (23 of these children had bronchopneumonia) the results were very satisfactory in 38. Within a week a great improvement was seen. The results in the children with uncomplicated cases were also very encouraging. In 43 of the 50 children the disease was markedly shortened; the frequency and severity of the paroxysms diminished quickly after the serum injections. Only six children died.

FROM THE AUTHOR'S SUMMARY.

DIPHTHERIA AS A GENERAL INFECTION. WERNER W. KRAUSA, Med. Klin. **45**:417 (April 7) 1950.

Some cases are cited of children and adults in whom diphtheria manifested itself as bronchitis and catarrhal bronchiolitis and pneumonia. Myocardial lesions, lesions in adrenal glands, liver, spleen and kidneys are cited as manifestations of this general infection. The frequent demonstration of diphtheria bacilli in the aspirated material from sternal punctures is emphasized.

AMBERG, Rochester, Minn.

CONTRIBUTION TO THE PATHOGENESIS OF NEURAL COMPLICATIONS OF MUMPS: PARALYSIS OF MUSCULUS SERRATUS WITH EPIDEMIC PAROTITIS. H. STUTTE, Med. Klin. **45**:432 (April 7) 1950.

About two to three weeks after both parotic glands began to swell, symptoms of involvement of the right arm appeared and progressed to paralysis of the right serratus muscle. The patient, a 20 year old woman, recovered completely within a year. Two other cases of mumps meningoencephalitis are cited; one in a 16 year old boy in whom the cerebral participation began four days after the parotitis became manifest, the other in a 35 year old woman in whom cerebral symptoms antedated the parotitis by a week. Stressing the time relations it is concluded that the lesions of the central nervous system are directly due to the mumps virus or its toxins and not to an antibody antigen reaction.

AMBERG, Rochester, Minn.

Acute Infectious Diseases

TYPHOID FEVER IN FOURTEEN CHILDREN TREATED WITH CHLORAMPHENICOL. WILLIAM A. REILLY and J. A. HARREL, JR., J. Pediat. **36**:440 (April) 1950.

Fourteen children with typhoid recovered promptly when treated with chloramphenicol. The initial dose of the drug was 50 mg. per kilogram followed by 125 to 250 mg. doses every two to three hours until fever disappeared and then every four to six hours during four to five days of normal temperature.

MACDONALD, Pittsburgh.

PERIARTERITIS NODOSA ASSOCIATED WITH RAT BITE FEVER DUE TO STREPTOBACILLUS MONILIFORMIS (ERYTHEMA ARTHRITICUM EPIDEMICUM). MARGARET PROUTY and ETHELDRED L. SCHAFER, J. Pediat. **36**:605 (May) 1950.

Prouty and Schafer describe a case of rat bite fever with positive agglutination for Streptobaccillus moniliformis in high titer. The patient was given penicillin without improvement. He continued on a progressive downhill course and died on the thirty-eighth day. Autopsy findings were typical of periarteritis nodosa. Whether the rat bite fever was concurrent with or antedated and perhaps initiated the periarteritis nodosa cannot be stated with certainty.

MACDONALD, Pittsburgh.

REACTIVATION OF RHEUMATIC FEVER BY SMALLPOX VACCINATION. PAUL FREUD, GEORGE D. ROOK and A. BRUNHOFER, J. Pediat. **36**:635 (May) 1950.

The authors think that smallpox vaccination can reactivate rheumatic fever. They report six cases to prove it.

MACDONALD, Pittsburgh.

AUREOMYCIN IN STAPHYLOCOCCEMIA, COMPLICATING AGRANULOCYTOSIS FOLLOWING TRIDIONE. GAYLE G. ARNOLD, J. Pediat. **36**:647 (May) 1950.

After five weeks of trimethadione U. S. P. (tridione®) therapy a Negro boy became sick with agranulocytosis, anemia and exfoliative dermatitis. The administration of trimethadione U. S. P. was stopped and aureomycin therapy was begun. Recovery was dramatic.

MACDONALD, Pittsburgh.

INFLUENZAL VACCINATION: EFFECT OF INTRACUTANEOUS IMMUNIZATION IN INFANTS AND CHILDREN. M. G. PETERMAN and V. KORES, Pediatrics **4**:337 (Sept.) 1949.

Forty-nine children from 4 months to 13 years of age were given 0.1 ml. influenzal vaccine types A and B intracutaneously. Serum antibody titers were determined before immunization and again four weeks after immunization. Considering a fourfold or more increase in serum antibody titer an indication of development of adequate immunity, the authors found that in the four month to two year old group 68 per cent developed a good response to type A and 81 per cent to type B. In the 2 to 5 year old group 100 per cent produced an adequate response to type A and 61 per cent to type B. In the 5 to 13 year old group 70 per cent produced a good response to type A and 65 per cent to type B. Reactions to the intracutaneous injection of the vaccine were mild and of little consequence.

FROM THE AUTHORS' SUMMARY.

ROCKY MOUNTAIN SPOTTED FEVER WITHOUT A RASH; REPORT OF A CASE TREATED WITH CHLORAMPHENICOL. ROBERT ORR WARTHEN and WILLIAM FOSTER BURDICK, Pediatrics **5**:930 (June) 1950.

A case of Rocky Mountain spotted fever that failed to develop a rash by the eighth day of the fever in spite of the delay in beginning specific chloramphenicol therapy until that time is reported. Owing to the absence of a rash the diagnosis of tick fever was only presumptive when chloramphenicol therapy was begun. It was established later, when the agglutination and complement fixation reactions became positive. Chloramphenicol effected recovery within 48 hours of its exhibition. There had been no previous immunization with Rocky Mountain spotted fever vaccine.

FROM THE AUTHORS' SUMMARY.

TETANUS PROPHYLAXIS WITH PENICILLIN-PROCAINE G. MILAN NOVAK, MILTON GOLDIN and WELTON I. TAYLOR, Proc. Soc. Exper. Biol. & Med. **70**:573 (April) 1949.

Since spores of Clostridium tetani are not infective in healthy tissue, a 5 per cent solution of calcium chloride was injected into Swiss mice as a tissue debilitant. Penicillin G procaine in oil with 2 per cent aluminum monostearate containing 300,000 units per milliliter was injected at various intervals into the animals. Both a reduction in mortality and a prolongation in life occurred in animals given penicillin G procaine prophylactically. The effect was more marked when the injections were made directly into the necrotic areas than when the same dose was injected at an uninfected site.

HANSEN, Galveston, Tex.

STUDIES IN PINWORM INFECTIONS. M. J. MILLER and L. P. E. CHOGNETTE, Canad. M. A. J. **62**:271 (March) 1950.

In part IV of a series of articles on this subject the authors discuss the use of parabenzylphenyl carbonate (diphenan). The percentage of cures was found to be low, and the authors consider the drug unsatisfactory in the present recommended doses.

McGUIGAN, Evanston, Ill.

CHANGES OF RESISTANCE OF ERYTHROCYTES IN MALARIA IN CHILDREN. SABIHA CURA, Ann. pædiat. **174**:247 (April) 1950.

The examination of the fragility of the red blood cells in malaria presented me with irregular results: an increased fragility was found as well as normal values.

I tried to find the same regular changes in the fragility of the red blood cells in children with malaria which Laser had observed in vitro after the addition of antimalarial drugs, but I could not discover any corresponding changes in fragility following antimalarial treatment with quinine, quinacrine (atabrine®), chlorguanide (paludrine®) and chloroquine (aralen®). I feel therefore that no conclusion should be drawn from the observations in vitro as to the therapeutic effect of these drugs in vivo or the kind of influence they may exert on the cycle of the malaria plasmodia.

FROM THE AUTHOR'S SUMMARY.

TREATMENT WITH AUREOMYCIN OF BRUCELLOSIS COMPLICATED WITH ENDOCARDITIS. F. H. ALBERS, Maandschr. v. kindergeneesk. **17**:382, 1950.

A report of a case of brucellosis combined with endocarditis is presented. The difficulty is pointed out of establishing the primary cause of this endocarditits, the Brucella bacteria or a Streptococcus of the viridans group. The latter was cultured from the blood. The patient was cured by treatment with aureomycin. FROM THE AUTHOR'S SUMMARY.

IS THE DEMONSTRATION OF TRICHOCEPHALUS EGGS IN THE STOOL WITHOUT SIGNIFICANCE? HELMUT BOEHNCKE, Med. Klin. **45**:436 (April 7) 1950.

A number of children were infested with Trichocephalus dispar and presented various symptoms, and among other diagnoses a diagnosis of appendicitis of periumbilical colic was made. Treatment with acetarsone (spirocid®) seems to promise well. The presence of trichuriasis is regarded as significant. AMBERG, Rochester, Minn.

BENEFITS AND DANGERS OF CHLORAMPHENICOL (CHLOROMYCETIN) IN THE TREATMENT OF TYPHOID AND PARATYPHOID. P. MOLLARET, Wien. klin. Wchnschr. **62**:381 (June 2) 1950.

On the whole, the treatment of typhoid and paratyphoid with chloramphenicol is very beneficial, but some strains of Salmonella can produce endotoxin and this endotoxin produces certain lesions in the guinea pig. Such lesions can also be produced in the guinea pig when after inoculation with an endotoxin rich strain of Salmonella chloramphenicol is administered. This may explain the fatal result following treatment in two cases. The psychic disorders seen during treatment seem to be preferable to a direct toxic action of the drug. In the author's experience the synthetic racemic chloramphenicol, which had to be given in double the dosage of the L substance for the antibiotic effect, produced a considerable increase of these disorders. A large initial dose is not recommended in treatment of Salmonella infections.

AMBERG, Rochester, Minn.

Chronic Infectious Diseases

THE DIAGNOSIS AND TREATMENT OF TUBERCULOUS MENINGITIS IN CHILDREN. EDITH M. LINCOLN and THOMAS W. KIRMSE, Am. J. M. Sc. **219**:382 (April) 1950.

The goal of treatment of tuberculous meningitis should be complete restitution to normal. Early diagnosis combined with prompt and adequate therapy are important factors in attaining this goal.

Lincoln and Kirmse report 18 cases of patients with tuberculous meningitis who have completed treatment with streptomycin and are continuing treatment with thiazolsulfone (promizole®) given orally. Thirteen children survived nine to 27 months after the initial diagnosis. All are mentally normal. Four have neurological residuals, none seriously crippling.

The addition of adequate amounts of thiazolsulfone to streptomycin would seem to be of advantage in the treatment of tuberculous meningitis. HENSKE, Omaha.

THE EFFECT OF STREPTOMYCIN UPON THE PATHOLOGY OF TUBERCULOUS MENINGITIS. WILLIAM J. WINTER, Am. Rev. Tuberc. **61**:171 (April) 1950.

The initial improvement frequently observed when tuberculous meningitis was treated with streptomycin is too often followed sooner or later by neurologic sequelae, with fatal consequences. It was found that these complications were directly related to two frequent pathologic findings, namely, ischemic and infective softening of the brain and the development of hydrocephalus.

Winter describes the pathologic findings in 12 streptomycin-treated patients, which he divides into three groups: those with acute disease, dying within two months and showing no clinical improvement; those with subacute disease, living three or four months with at least a short interval of improvement, and those with chronic disease, having definite clinical remission before fatal relapse. The pathologic changes encountered in these cases apparently occur in the following order: progressive organization of the exudate in the subarachnoid space;

early dissolution of fibrin and replacement by chronic inflammatory cells—the foci of necrosis tend to be either encapsulated or partially infiltrated by fibroblasts—acute tuberculous arteritis, commonly involving the circle of Willis and proximal branches of the middle cerebral arteries, resulting in a proliferative endarterial reaction causing severe stenosis or occlusion of the vessels. Multiple ischemic softenings in the basal ganglions and internal capsule resulting from the endarteritis are a common source of neurologic sequelae.

The outstanding complications found were communicating hydrocephalus and multiple ischemic softening of the brain. Spinal block may develop owing to extensive fibrous organization of the meningeal exudate in the vicinity of the site of intrathecal injections of streptomycin.

EUGENE SMITH, Ogden, Utah.

NEUROLOGIC COMPLICATIONS FOLLOWING THE MANTOUX TEST. F. T. MÉREI, Arch. Neurol. & Psychiat. **63**:249 (Feb.) 1950.

One case of pontile encephalitis and 2 cases of multiple sclerosis are reported as having followed by a few days the performance of Mantoux tests. It is felt that in 1 case the inoculation may have reactivated a preexisting lesion.

McGUIGAN, Evanston, Ill.

TREATMENT OF MILIARY AND MENINGEAL TUBERCULOSIS IN INFANTS AND CHILDREN. THOMAS L. PERRY, California Med. **72**:159 (March) 1950.

Streptomycin and combined streptomycin-thiazolsulfone (promizole®) treatment of miliary and meningeal tuberculosis in infants and children at the Los Angeles Children's Hospital has resulted in clearcut arrests of the disease in seven patients, two of whom had tuberculous meningitis. A much longer period of observation will be necessary before these patients may be considered cured. These results are incomparably better than the universally fatal outcome of both diseases in a large and unselected group of untreated patients which has been studied. Thiazolsulfone, and possibly also paraaminosalicylic acid, should be given concurrently with streptomycin. As they are relatively harmless drugs, they should be given to ambulatory patients for a long period of time after arrest of the disease to decrease the likelihood of recurrence. If necessary, streptomycin may be given for longer than 90 days or in second courses, since combined chemotherapy apparently delays the appearance of streptomycin-resistant strains of tubercle bacilli. The current pessimism with which many pediatricians view miliary and meningeal tuberculosis is unwarranted. Optimism will be rewarded with many more recoveries in the future.

PRYOR, Redwood City, Calif.

PROLONGED SURVIVAL FOLLOWING STREPTOMYCIN THERAPY OF TUBERCULOUS MENINGITIS. HALL S. TACKET and GEORGE S. LOVEJOY, J. A. M. A. **142**:648 (March 4) 1950.

Another patient with tuberculous meningitis treated with streptomycin was restored to normal activity only to succumb to that disease 27 months later after the third admission to the hospital.

KIMBALL, Evanston, Ill.

STREPTOMYCIN AND PROMIZOLE COMBINED THERAPY IN TUBERCULOUS MENINGITIS IN CHILDREN. T. F. SU and M. Y. WU, J. Pediat. **36**:295 (March) 1950.

Streptomycin (given intramuscularly and intrathecally) combined with thiazolsulfone (promizole®) (given orally) was more effective in the treatment of tuberculous meningitis than streptomycin alone. Sixteen patients were given combined therapy, and at the time of this report, all were alive. Six patients were given streptomycin alone; of these 2 were improved, 1 was unimproved and 3 died. Reactions to streptomycin were frequent in both groups.

MACDONALD, Pittsburgh.

IMMUNOLOGIC ASPECTS OF BCG VACCINATION. SOL ROY ROSENTHAL, J. Pediat. **36**:399 (April) 1950.

BCG vaccination by the multiple puncture method is a safe and effective adjunct to accepted methods of tuberculosis control, such as early diagnosis and isolation of the source case.

The response of newborn infants is prompt with conversion of the tuberculin reaction in 11 to 13 days to one month and persistence of this reaction for at least 5½ years. BCG vaccination helps to prevent primary infection and also minimizes hematogeneous sequelae such as tuberculous meningitis and miliary tuberculosis. Rosenthal reports a study of 131 vaccinated infants and 128 nonvaccinated controls. In three of the vaccinated infants roentgenographic evidence of tuberculosis developed, all recovered and all showed calcification according to their roentgenograms. In the control group, six children became sick with tuberculosis and three died.

MACDONALD, Pittsburgh.

CYSTIC TUBERCULOSIS OF BONE COMPLICATED BY TUBERCULOUS MENINGITIS. EUGENE KUTZ, STANLEY MACHT and R. EASTON, J. Pediat. **36**:550 (May) 1950.

Few cases of multiple cystic bone tuberculosis have been reported, and until 1949 none had been reported with complicating tuberculous meningitis. The cases reported here are the second and third cases of this type in the literature. Treated with streptomycin and thiazolsulfone (promizole®), the meningitis cleared in both cases and there was roentgen ray evidence of healing of the bone lesion.

MACDONALD, Pittsburgh.

TREATMENT OF TUBERCULOUS MENINGITIS WITH STREPTOMYCIN. A. ARIZTIA, M. LATORRE and A. VARGAS, Helvet. paediat. acta **5**:18 (March) 1950.

Of 43 children treated for tuberculous meningitis 13 died, 20 made a complete recovery and 10 are still under treatment with a favorable prognosis. The children were under observation from six months to three years. Treatment in all cases consisted of combined intramuscular and intrathecal administration of streptomycin. Thirty-five of the 43 children had, in addition, a tuberculous infection of some other organ. Improvement in all cases was first shown on the clinical side; the cerebrospinal fluid returned to normal at a later date. A description is presented of the symptoms of chronic tuberculous meningitis and its residual lesions. The pathologic histology of the lesion is discussed, and particular emphasis is put on the presence of hydrocephalus and its causation by mechanical obstruction of the circulation. A number of apparently paradoxic neurologic symptoms may be explained by hydrocephalus and by the varying degree of obstruction which the exudate produces in the region of the isthmus.

FROM THE AUTHORS' SUMMARY.

USE OF PARAAMINOSALICYLIC ACID AND ITS SODIUM SALT IN TREATMENT OF CHILDHOOD PULMONARY TUBERCULOSIS. U. PELLEGRINI and G. MAINI, Lattante **21**:1 (Jan.) 1950.

Paraaminosalicylic acid in doses of 0.4 to 0.5 Gm. per kilogram of body weight per day divided into eight doses, one every three hours, was well tolerated by children. The drug acted quickly to overcome the toxicity and fever of the allergic-exudative type of tuberculosis; the pulmonary changes, as manifested by roentgenograms, responded much more slowly.

HIGGINS, Boston.

PENICILLIN IN CONGENITAL SYPHILIS IN THE INFANT. JULIO MENEGHELLO and JORGE ROSSELOT, Rev. chilena de pediat. **21**:13 (Jan.) 1950.

The authors report 12 cases of malnourished infants hospitalized with the diagnosis of congenital syphilis who were treated with either penicillin in oil or penicillin in procaine and aluminum monostearate. They established their own plan of treatment, consisting of two or three penicillin injections, spaced every forty-eight or seventy-two hours, with a total dose of 100,000 to 436,000 units per kilogram of body weight. No important therapeutic incidents were noted, and no deaths occurred. The authors obtained immediate specific regressions, similar to those obtained with other forms of penicillin treatment. There was noted only 1 clinical and serologic relapse; in this case there was rapid response to a second treatment, with slow-acting penicillin. The authors recommend a second course of treatment also with slow-acting penicillin when the different tests present evidence of a presumptive syphilitic activity that might suggest a probable relapse.

FROM THE AUTHORS' SUMMARY.

SEDIMENTATION RATE IN OSTEOARTICULAR TUBERCULOSIS. EUGENIO DIAZ BORDEU, Rev. chilena de pediat. **21**:28 (Jan.) 1950.

The author studied the sedimentation rate in bone tuberculosis and its relation to the general and the local process and different treatments; he concludes that because of the many factors concerned the prognostic and diagnostic value is questionable.

FROM THE AUTHOR'S SUMMARY.

STATISTICS OF THE BONE AND JOINT TUBERCULOSIS FROM THE YEARS BEFORE AND AFTER THE SECOND WORLD WAR. RUDOLF VOLKERT, Med. Klin. **45**:304 (March 10) 1950.

The number of cases of bone and joint tuberculosis seen at the dispensary of the orthopedic clinic in Munich during a three year period from 1936 through 1938 are compared with those during a period from 1946 through 1948. The number of the last three years is much greater mainly because of an increase in tuberculous spondylitis. Figures are given for the age group 0 to 4 years, 4 to 14 years, 14 to 20 years and beyond. The incidence of spondylitis was greatest in the 14 to 20 year group. The maximum for gonitis and coxitis tuberculosa falls into the 4 to 14 years group.

AMBERG, Rochester, Minn.

THE PRESENT STAND ON THERAPY OF TUBERCULOUS MENINGITIS AND ITS RESULTS IN THE CHILDREN'S HOSPITAL OF ZURICH. ETTORE ROSSI, Helvet. paediat. acta **5**:27 (March) 1950.

The Children's Hospital in Zurich began three years ago to treat tuberculous meningitis with streptomycin. A synopsis and critical analysis of the results obtained is presented. The technic and methods are described in great detail. Failures in treatment are due mainly to delay in hospitalization and to the very young age of the patients. From a close study of the patients' histories it appears that treatment with streptomycin in combination with paraaminosalicylic acid is of great value.

FROM THE AUTHOR'S SUMMARY.

Diseases of Blood, Heart and Blood Vessels and Spleen

CARDIAC HYPERTROPHY IN EXPERIMENTAL ARTERIOVENOUS FISTULA. HERMANN WIPF and HUGH BRAWNER, Arch. Path. **48**:405 (Nov.) 1949.

Wipf and Brawner constructed a surgical fistula between the common carotid artery and the external jugular vein in 11 dogs. In those dogs in which the fistula was maintained for three months no significant hypertrophy of the heart developed.

CHAN, San Francisco.

NONLIPID RETICULOENDOTHELIOSIS: LETTERER-SIWE DISEASE; REPORT OF A CASE. WALTER J. LEVINSKY, Arch. Path. **48**:462 (Nov.) 1949.

The case of an 11 month old white girl is reported, who exhibited the syndrome of Letterer-Siwe's disease. The rapid, fatal illness was preceded three weeks by an upper respiratory tract infection which responded to sulfonamide therapy. The onset was acute and characterized by hemorrhagic phenomena, fever, splenomegaly, hepatomegaly and severe anemia. There was no familial history. Acute leukemia was suspected at the time of admission on the basis of the clinical findings, and a white blood cell count of 41,000 with numerous "blast" forms was noted in the peripheral smear. In addition to other immediate therapy, 1 mg. of aminopterin was given. A competent hematologist reviewed the peripheral blood smears and other smears and noted that the previously noted "blast" forms were in reality nucleated red cells. Four bone marrow aspirations were made. Only the last two showed remarkably large cells suggesting a lipid storage disease. A skeletal survey showed only minor nonspecific demineralization of the metaphysial areas of several of the long bones. The spleen was removed before the nature of the disease was determined, but the organ was too effaced by hemorrhage, infarction and hematopoieses to permit proper evaluation of the presence of large histiocytes in the dilated sinusoids. Autopsy bore out the diagnosis of Letterer-Siwe's disease. Atypical mononuclear cells were seen in lymph nodes, liver, spleen, thymus, dermis of skin, submucosa of large intestines, pleura, interlobar septum of

lung and bone marrow, with complete destruction of normal architecture. The amount of aminopterin given was considered too small to affect the clinical course and the gross and microscopic observations. Levinsky believes that the disease was initiated by the infectious process, which is in keeping with the concept of some physicians that this disease is caused primarily or secondarily by infection. Levinsky also believes that some of the clinical features suggest that Letterer-Siwe's disease, Schüller-Christian's disease and eosinophile granuloma represent similar types of a fundamental basic disorder of the reticuloendothelial system.

CHAN, San Francisco.

CONGENITAL MITRAL ATRESIA. H. LEE LARGE, JR., M. Sc. **219**:268 (March) 1950.

Two cases of congenital atrioventricular septal, shift to the left, one with mitral atresia, are reported.

From the relation between mitral atresia, or stenosis, and the associated anomalies it is concluded that hypoplasia of the left atrium lends strong support to Mönckeberg's shift to the left hypothesis.

A patent ductus arteriosus is so commonly associated with congenital mitral atresia that it may be taken to be an intrinsic part of the composite anomaly.

Previously offered explanations for the pathogenesis of the patent ductus arteriosus and the infantile type of aortic coarctation are consistent with the findings in our cases.

HENSKE, Omaha.

PRENATAL FIBROELASTOSIS ("FETAL ENDOCARDITIS") MANIFESTED CLINICALLY BY TOTAL HEART BLOCK. HAROLD E. STADLER and CHARLES A. REID, J. Pediat. **36**:370 (March) 1950.

Stadler and Reid report a case of fetal and neonatal bradycardia associated with electrocardiographic evidence of total heart block. The patient died suddenly at the age of 3 months. At autopsy the heart showed endocardial fibroelastosis. A focal pericarditis was present. The authors express the opinion that the changes are those of a prenatal inflammatory process.

MACDONALD, Pittsburgh.

A STUDY OF THE Q-T_c INTERVAL IN THE ELECTROCARDIOGRAM IN RHEUMATIC FEVER. NATHAN EPSTEIN and JAMES D. GARDAM, J. Pediat. **36**:583 (May) 1950.

Prolongation of the Q-T_c interval is not diagnostic of active rheumatic carditis. This sign is no more sensitive than the accepted abnormal electrocardiographic evidence of acute carditis. Furthermore, the Q-T_c interval may be elevated in about one third of the patients with inactive carditis.

MACDONALD, Pittsburgh.

CONGENITAL ARTERIOVENOUS FISTULA OF THE CERVICAL VERTEBRAL VESSELS WITH HEART FAILURE IN AN INFANT. JOHN A. NORMAN, KENNITH W. SCHMIDT and J. GROW, J. Pediat. **36**:598 (May) 1950.

The authors present a case of arteriovenous fistula involving the cervical portion of the left vertebral vessels in a 6 month old infant. There was associated heart failure. Ligation and excision of the fistula resulted in complete recovery.

MACDONALD, Pittsburgh.

SICKLE CELL ANEMIA IN YOUNG INFANTS. GRADY E. BLACK, J. Pediat. **36**:621 (May) 1950

Black reports a case of sickle cell anemia occurring in a 3 month old infant and in a 7 month old infant. The disease is rarely recognized in infants.

MACDONALD, Pittsburgh.

SURGICAL TREATMENT OF COARCTATION OF THE AORTA. GORDON MURRAY, Canad. M. A. J. **62**:241 (March) 1950.

Surgical correction of coarctation has given good results in 5 patients. It is felt that in patients under 20 years of age with symptoms of hypertension and cardiac enlargement the operation offers good prospects for improvement.

MCGUIGAN, Evanston, Ill.

OCULAR FINDINGS IN CONGENITAL HEART DISEASE. J. L. KYLE, Canad. M. A. J. **62**:263 (March) 1950.

The author examined the fundi of 30 children having congenital heart disease. Cyanosis retinae was most marked in cases of tetralogy of Fallot and Eisenmenger's syndrome and was proportional to the degree of polycythemia.

McGUIGAN, Evanston, Ill.

THE ACTION OF THE ANTIBIOTICS, ESPECIALLY PENICILLIN, ON THE RHEUMATIC CARDITIS IN INFANTS. P. PINNA, Ann. ital. di pediat. **3**:53 (Feb.) 1950.

In order to study the action of antibiotics in cardiac rheumatic localizations, Pinna has treated 21 children with penicillin, four of whom were treated with streptomycin also.

As he did not remark any great difference between the results of this treatment and the results observed in subjects treated with salicylate alone or associated with other remedies, excluding the antibiotic, he thinks that the action of the antibiotic used by him in rheumatic disease is very light or none.

Great attention must be paid to five children in whom suddenly appeared symptomatology of acute coronaritis and myocardial infarct, in which an aggravation was noticed when penicillin was used, suggesting that penicillin may sometimes contribute, with a toxic or allergic mechanism, to aggravate a coronary condition already caused by the rheumatic disease.

FROM THE AUTHOR'S SUMMARY.

TWO CASES OF SPLENOMEGALY OF THE FIBROUS-CONGESTIVE TYPE. P. BUONOCORE, Pediatria **58**:62 (Jan.) 1950.

The onset of each of these 2 cases of splenomegaly of the congestive fibrous type was shortly after birth. The cause in one case was apparently a congenital heart lesion and in the other, an infection of the umbilical cord. Each child had frequent hematemesis and died after a hematemesis. This splenomegaly should be regarded as a separate entity from Banti's disease.

HIGGINS, Boston.

FAMILIAL HEMOLYTIC JAUNDICE WITH AND WITHOUT ALL THE USUAL SIGNS. V. D. BORI, Policlin. inf. **16**:589 (Dec.) 1948.

Case histories are given of a father and his three children, each of whom had a constitutional hemolytic disease (Minkowski-Chauffard syndrome). Not all of them showed all the signs of the syndrome; one had only slight enlargement of the liver and spleen; two showed no jaundice and no uribilinuria; one had a negative van den Bergh reaction.

HIGGINS, Boston.

EXSANGUINATION TRANSFUSIONS IN CHILDREN: DESCRIPTION OF AN AUTOMATIC APPARATUS. G. SANSONE and C. TADDEI, Policlin. inf. **16**:625 (Dec.) 1948.

A new type of automatic apparatus devised by the authors is described. Ten children thus far have received exsanguination transfusions with this apparatus; two of the children had hemolytic disease of the newborn, six had leukemia and two had Cooley's anemia. Technically, all the transfusions were successful. The authors conclude that exsanguination transfusions are a very valuable therapeutic measure in cases of hemolytic disease of the newborn. They also hope that more understanding of the pathology of Cooley's anemia may result from these transfusions.

HIGGINS, Boston.

CHRONIC COR PULMONALE FROM THORACIC DEPRESSION. ALBERTO GRASSI, Riv. di clin. pediat. **48**:69 (Feb.) 1950.

Grassi describes a case of chronic cor pulmonale in a 7 year old child. The condition was caused by introflexion of the thorax with total displacement of the heart to the right. Differential diagnosis of cor pulmonale from dextrocardia was based principally on roentgenologic and electrocardiographic examinations.

The clinical findings are described and were especially characterized by pulmonary insufficiency and hypertension with relapsing bronchopneumonia which resolved very slowly.

The etiological and pathogenetic problem is discussed.

FROM THE AUTHOR'S SUMMARY.

PAROXYSMAL TACHYCARDIA IN AN INFANT. JULIO GUASCH and ROBERTO SCHIFFRIN, Rev. chilena de pediat. **21**:125 (March) 1950.

The literature on paroxysmal tachycardia in infancy is reviewed with stress on the rarity of this condition.

The case history of a 1 month old infant who presented the clinical and electrocardiographic findings of a supraventricular paroxysmal tachycardia is presented.

Guasch and Schiffrin comment on the spectacular response to the intravenous administration of neostigmine (prostigmin®).

FROM THE AUTHORS' SUMMARY.

FAMILIAL DERMOCHONDROCORNEAL DYSTROPHY. JULES FRANCOIS and CLEMENT DETRAIT, Ann. paediat. **174**:145 (March) 1950.

The authors report observations on 2 children, a girl of 12 years and her brother of 11. Both presented a triple syndrome: a subepithelial central dystrophy of the cornea, xanthomas of the skin and an osteochondral dystrophy localized in the distant parts of the extremities.

The presence of large xanthomatous foam cells inside the corneal lesions as well as in the cutaneous nodules induced the authors, in spite of a normal cholesterol level in the blood, to relegate this syndrome into the order of the lipoidoses, especially since the skin nodules had the clinical appearance of xanthomas and contained cholesterol.

FROM THE AUTHORS' SUMMARY.

A NEW NATURAL DEFICIENT NONSPECIFIC FACTOR: THE BLOOD PLASMA LIPASE; ITS PROGRESS AND THERAPEUTIC VALUE IN INFECTIONS AND INTOXICATIONS. G. SOLARINO, Bull. d. Schweiz. Akad. d. med. Wissensch. **6**:84 (March) 1950.

Authors who have previously studied this problem have concluded that the plasmolipase index can be correlated only with metabolic variations.

Since 1942, prolonged and systematic observations have been made at the General Pathological Institute, Bari, on the blood of more than 100 hospitalized tuberculous patients. Observations were continued for a long time (sometimes for three years) until death or clinical recovery occurred. It was found that the variation in the tributyrolytic power of the blood plasma not only reflects the metabolic rate but is also a precise index of the defensive power of the organism; it has an absolute and overwhelming diagnostic significance in tuberculosis, even if it does not agree with the clinical findings. Moreover, in the course of investigations carried out in the same institute on the behavior of the blood plasmolipase during the treatment with sulfonamides of diseases due to pyogenic germs, an increase in the lipase index of the plasma has been observed coinciding with recovery or with improvement due to sulfonamide therapy. In an analogous manner, in chronic experimental poisoning with uranium nitrate, it has been possible to demonstrate a slow and progressive increase in the tributyrolytic value of the blood plasma coinciding with the appearance of habituation to the poison and with the disappearance of the characteristic nephrosis.

The results of systematic titration of the blood lipase during vaccination seem rather interesting. All these recent observations enable one to conclude that the blood plasmolipase is a true, nonspecific defense factor coupled with the globulin fraction of the blood plasma and endowed with protective properties for the organism during infections and toxic states.

It now only remains for us to determine the genesis of this factor (still a matter of dispute). Is it purely humoral or perhaps mixed, cellulohumoral? From a series of personal observations made by Solarino, the latter is inclined to believe that the tributyrolytic blood lipase is—at least to a large extent—of lymphocytic origin.

FROM THE AUTHOR'S SUMMARY.

THE USE OF PLACENTAL BLOOD FOR TRANSFUSIONS. C. VERCESI, Bull. d. schweiz. Akad. d. med. Wissensch. **6**:141 (March) 1950.

The transfusion of placental blood was proposed for the first time in 1934 by Maurizio Ascoli and Carlo Vercesi. A little later, the same method was proposed by Russian scientists, but by force of circumstances the exchange of scientific ideas between Italy and Russia was suspended, and it was not until the end of the war that it was possible to become acquainted with the work done on this subject abroad and in Italy. The experience gained abroad has certainly been important, and the problem has been attacked from several angles, including a study of the biologic characteristics of placental blood (studied not only in Russia but also in North and South America), methods of removal and clinical usage.

Papers published in Italy are not numerous. Nevertheless, especially of late, some important and valuable publications have appeared, such as those of the Padua Obstetrical Clinic (director, Professor Vercesi). By careful work and an appropriate technic, these have brought to light all the biologic aspects of placental blood and particularly questions relating to its use in transfusions. The technic of withdrawal and preservation of the blood itself has been rendered practical and accessible even to institutes possessing only modest equipment. The type of blood transfused has been carefully controlled and its qualitative effects, in particular, have been demonstrated.

According to the records collected by the Padua school, placental blood possesses numerous specific properties and can be used for the reconstruction of the blood in secondary anemia, for the treatment of metrorrhagia in puberty or as an antiseptic and antitoxic factor in states of malnutrition and advanced cachexia in malignant tumors. In cases of shock and gestational toxicosis, placental blood or plasma effectively combats the hypoproteinemia.

FROM THE AUTHOR'S SUMMARY.

DIAGNOSIS OF OPEN DUCTUS ARTERIOSUS (BOTALLI). O. BAYER and H. C. LANDEN, Schweiz. med. Wchnschr. **80**:261 (March 11) 1950.

Procedures are emphasized which permit a diagnosis of open ductus arteriosus without angiocardiography and catheterization of the heart. It is stated that the dilatation of the conus pulmonalis is not so common in adults as has been generally assumed; it is seen more frequently in children. A diminution of the murmur in the second left interspace or its disappearance on the Valsalva test can occur. The blood pressure at rest and after exercise may be of some value. Preoperative and postoperative examples are given. Vital capacity is diminished, the minute respiratory volume at rest is increased and decreased by several liters on inhalation of oxygen. After operation the respiratory volume diminishes, and the decrease on inhalation of oxygen is very much less. The observations were made on 5 patients 17 to 28 years of age.

AMBERG, Rochester, Minn.

PRESENCE IN LEUKEMIC BLOOD PLASMA OF FACTORS CAPABLE OF CHANGING THE LEUKOCYTIC BLOOD PICTURE OF NORMAL PERSONS. GUISEPPE OLIVA and CORRADO TRAMONTANA, Schweiz. med. Wchnschr. **80**:306 (March 25) 1950.

Oxalated blood plasma obtained from patients with myelogenous leukemia injected intravenously into normal volunteers produced a considerable increase of leukocytes, mainly of neutrophile granulocytes and in some cases with appearance of myelocytes. When plasma obtained from patients with lymphatic leukemia was used, the number of lymphocytes increased mainly. Plasma subjected to irradiation with roentgen rays was much less effective.

AMBERG, Rochester, Minn.

BONE MARROW INJURY AND PANHEMOCYTOPENIA DUE TO HYDANTOIN COMPOUNDS. J. ROHRBACH, Schweiz. med. Wchnschr. **80**:337 (April 16) 1950.

The cases of five patients with epilepsy are reported. After treatment with hydantoin compounds, all presented injury of the bone marrow with severe blood changes in the sense of a panhematopenia. Three patients recovered completely. Two died, one of these a 13 year old boy. In three cases diphenylhydantoin (dilantin®) preparations were given; in two, 2-methyl-5, 5-phenylethyl hydantoin (mesantoin®) preparations.

AMBERG, Rochester, Minn.

THE PRACTICAL SIGNIFICANCE OF THE RHESUS FACTOR FOR BLOOD TRANSFUSIONS. H. BRUTSCH and B. CATHOMAS, Schweiz. med. Wchnschr. **20**:513 (May 20) 1950.

In regard to two patients, a man 66 years of age and a woman 63 years of age, who reacted with hemolysis on repeated transfusions, the importance of the Rh factors is discussed. One of the patients was sensitized to Rh_0 and the other, to the antigen. Of these the Rh_0 factor is the more important, and measures are given to avoid hemolysis after transfusion.

AMBERG, Rochester, Minn.

Diseases of Nose, Throat and Ear

USE OF THIOPENTAL SODIUM U. S. P. (SODIUM PENTOTHAL) IN OPERATIONS ON EAR, NOSE AND THROAT. GILBERT E. FISHER and LAWRENCE S. WOODLEY, Arch. Otolaryng. **50**:295 (Sept.) 1949.

Thiopental sodium is a useful anesthetic in operations on the ear, nose and throat of adults but is not used in children under 15 years.

KIMBALL, Evanston, Ill.

RHABDOMYOSARCOMA OF THE MIDDLE EAR. SAFA KARATAY, Arch. Otolaryng. **50**:330 (Sept.) 1949.

The history, course, operation and autopsy findings in a case of rhabdomyosarcoma arising from the middle ear of a 3½ year old Negro girl are reported.

KIMBALL, Evanston, Ill.

A STUDY OF THE RELATIONSHIP BETWEEN MEASURED HEARING LOSS AND INTELLIGIBILITY OF SELECTED WORDS. BRUCE M. SIEGENTHALER, J. Speech & Hearing Disorders **14**:111 (June) 1949.

Five subjects with audiograms indicating about equal loss of acuity for the frequencies 128 through 8192 cycles per second, 5 subjects with a greater loss of acuity for high frequencies than for low and 5 subjects with hearing acuity within normal limits for all pure tones tested were tested on a standardized master word list at the threshold of intensity for each group of subjects. The concept that an equal amount of hearing loss for pure tones usually tested with the pure tone audiometer has the effect of simply raising the threshold for speech is not supported by the experimental results. Persons with different patterns of hearing acuity for pure tones give different and distinctive patterns of responses to voicing of consonants, pressure patterns of consonants and the influences of one sound on another within a word.

PALMER, Wichita, Kan. [ARCH. OTOLARYNG.]

HOME TRAINING FOR PRESCHOOL DEAF CHILDREN THROUGH CORRESPONDENCE. HARRIET ANDREWS MONTAGUE, J. Speech & Hearing Disorders **14**:131 (June) 1949.

The home correspondence course from the John Tracy Clinic, of Los Angeles, for parents has been mailed over a period of six years to more than 2,000 families. Sixty-five per cent of those who enrolled completed the course. About 75 per cent finished at least the first six instalments with varying benefits. The author states that good results were obtained by those who utilized the course conscientiously and intelligently.

PALMER, Wichita, Kan. [ARCH. OTOLARYNG.].

A SPEECH AND HEARING PROGRAM FOR CHILDREN IN A RURAL AREA. HARRIET M. DUNN, J. Speech & Hearing Disorders **14**:166 (June) 1949.

This article is a review of a speech and hearing program in rural Vermont. Diagnostic speech and hearing clinics are held weekly in four cities accessible to rural areas. Follow-up work, including certain types of medical care and provision of transportation to classes, help in solving certain social problems. Classes in speech correction and auditory training are held three days a week at the center in Rutland. An eight week intensive training program is carried on in a summer residence center for children with speech and/or hearing disorders.

PALMER, Wichita, Kan. [ARCH. OTOLARYNG.].

RADIOLOGIC STUDY OF THE MASTOID BONE IN INFANTS IN CONJUNCTION WITH ANATOMIC AND PATHOLOGIC INVESTIGATIONS. HENRY G. KOIRANSKY, IRVING K. ETTMAN and EDWARD L. WHITE, N. Y. State J. Med. **49**:1291 (June 1) 1949.

The authors undertook to determine roentgenologically the earliest age at which definite mastoid cells are present. They made roentgenograms of infants from birth to 1 year and determined that the mastoid process is absent or minute at birth. A divergence of opinion with Cheatle, Albrecht and Wittmaack, who are quoted, is manifest: These authors noted "that pneumatization of the mastoid began to appear at about six months" and was definite after seven months. However, there was inequality on the two sides in many patients. A study of a stillborn child weighing 15 pounds (6,804 Gm.) and delivered by cesarean section was made, first roentgenographically and then with stained sections in series after decalcification; various "outpointings" from the mastoid antrum into the mastoid process were observed, which were regarded as primary mastoid cells with a lining membrane continuous from the middle ear cavity. From this the authors conclude that "cellular invasion may occur even in the newborn." Bacterial invasion can also take place by the same route; hence, the value of early administration of antibiotics in all acute infections in infancy and childhood, a factor well understood by pediatricians. The conclusion is that formation of mastoid cells is more a matter of physical development than of the chronologic age of the individual child. Six references to the literature and one figure are included.

VOORHEES, New York [ARCH. OTOLARYNG.].

ANTIHISTAMINES AND THE CATARRHAL CHILD. C. T. PIPER, Clin. Rep. Adelaide Children's Hosp. **1**:266 (Nov.) 1949.

Studies of 18 patients with infections of the upper respiratory tract treated with diphenhydramine (benadryl®) hydrochloride are presented. Unusual results were not observed.

McGUIGAN, Evanston, Ill.

OTOSCLEROSIS IN IDENTICAL TWINS. GERALD M. FOX, South African Med. J. **24**:325 (May 6) 1950.

Otosclerosis occurring in identical twins is reported. Both were treated by fenestration. This is considered the first case in which fenestration was done on twins.

McGUIGAN, Evanston, Ill.

Diseases of Lungs, Pleura and Mediastinum

CHLOROMYCETIN IN TREATMENT OF PNEUMONIA IN INFANTS AND CHILDREN: A PRELIMINARY REPORT OF THIRTY-THREE CASES. ADRIAN RECINOS, JR., SIDNEY ROSS, BENNETT OLSHAKER and ELLSWORTH TWIBLE, New England J. Med. **241**:733 (Nov. 10) 1949.

Chloramphenicol (chloromycetin®) is an antibiotic derived from a strain of Streptomyces venezuelae. Its antimicrobic spectrum includes rickettsia, certain viruses, gram-positive cocci, gram-negative organisms which include some of the coliform group, Eberthella typhosa and Shigella. It is absorbed from the stomach. It cannot be given parenterally, but partial rectal absorption takes place.

The authors treated 33 children with pneumonia with chloramphenicol. The drug was given orally every three hours, the average dose being 110 mg. per kilogram a day in eight divided doses. The average duration of treatment was a little more than 4 days. Older children took a capsule well; young children were given the powder mixed in aromatic eroidictyon syrup (aromatic yerba santa syrup®). The therapeutic effect of chloramphenicol on these 33 patients with bacterial pneumonia was favorable, although empyema in one patient required surgical drainage before recovery ensued. Normal temperatures were attained in two thirds of the patients in 18 hours and in all but one patient by three days. Other vital statistics concerned with the pneumonic process reflected the salutary effect of the drug. Leukopenia was observed in several patients three to five days after the start of the treatment, but the administration of the drug was continued with no resultant ill effects.

Since an approximately equal number of patients ill with bacterial pneumonia were treated with aureomycin, their progress was compared to that of the chloramphenicol-treated group.

There were no statistical differences in the general response to treatment of either group. Practically, chloramphenicol appeared to initiate fewer disagreeable gastrointestinal symptoms than did aureomycin.

Chloramphenicol may be regarded as an effective drug in the therapy of bacterial pneumonia as it occurred in the patients described.

WHEELOCK, Denver.

BRONCHIECTASIS. LAWRENCE MISCALL, New York State J. Med. **49**:1070 (May 1) 1949.

Miscall analyzes 146 cases of clinical bronchiectasis recorded in the thoracic service at Bellevue Hospital. Ten per cent of the patients were under 20, and 62 per cent were under 50. There were instances of constant cough, copious foul sputum, recurrent pneumonia, hemoptysis, abscess and empyema. Of the 146 patients, only 44 were operated on.

The lack of attempts at curative therapy contributes to marked deterioration of the entire system. Medical care calls for rest in bed, adequate diet reenforced with proteins, vitamins and minerals and intravenous administration of blood to overcome the anemia and asthenia. Sinusitis and oral sepsis should be diagnosed and overcome. Bronchoscopy should be routinely practiced for diagnosis and treatment. The removal of secretions by suction brings relief, and dried exudate, granulations, foreign bodies, etc., may be found and treatment carried out accordingly. Tumors and stenosis usually call for a change of treatment.

Cardiorespiratory considerations influence operability. The younger patients usually present more operable conditions than the older ones. Surgical intervention should be carried out promptly once the matter of operability is settled. The best time for the operation is when the sputum is reduced in quantity and its quality is less dangerous. In some cases, preliminary drainage and secondary excision offer more than the one stage procedure with extensive removal of lung substance. The intrahilar dissection technic is recommended. The safety of lobectomy or segmental resection is stressed, the mortality being only 2 per cent.

VOORHEES, New York [ARCH. OTOLARYNG.].

PRODUCTION OF ACUTE PULMONARY EDEMA BY AMMONIUM SALTS. HAROLD KOENIG and RUTH KOENIG, Proc. Soc. Exper. Biol. & Med. **70**:375 (March) 1949.

The administration of ammonium salts (ammonium chloride, nitrate, bromide, sulfate and acetate) to guinea pigs, white rats and cats in toxic amounts resulted in acute pulmonary edema. Rabbits did not appear to be susceptible to pulmonary edema due to ammonia. Acidosis was not a factor in producing pulmonary edema. The findings of ammonium intoxication were chiefly dyspnea, muscle fasciculations and convulsions; at autopsy they were pulmonary edema and congestion with a variable degree of hemorrhage and moderate dilatation of the right ventricle, right atrium and places of entrance of the venae cavae. Edema, congestion and hemorrhage were found on microscopic study.

HANSEN, Galveston, Texas.

THE TREATMENT OF THE BRONCHOPNEUMONIA OF YOUNG INFANTS BY STREPTOMYCIN. R. BULGARELLI and P. DURAND, Policlin. inf. **16**:636 (Dec.) 1948.

In the years 1945 to 1948, in the pediatric clinic of Genoa, 38 per cent of the infants with bronchopneumonia died in spite of sulfonamide and penicillin therapy. Since gram-negative bacteria were very frequently responsible for the disease, streptomycin therapy was started. The mortality when streptomycin alone was used was 25 per cent; when a combination of streptomycin and penicillin was used, the mortality was still further lowered to 19 per cent.

HIGGINS, Boston.

Diseases of the Gastrointestinal Tract, Liver and Peritoneum

HEPATIC LESIONS PRODUCED BY LEAD IN RATS FED A HIGH FAT DIET. HUGO CHIODI and BULGARELLI and P. DURAND, Policlin. inf. **16**:636 (Dec.) 1948.

Authors do not agree on the importance and constancy of the hepatic injuries produced by lead, and various forms and degrees of damage have been described. Blackman found liver cell damage in 21 cases of poisoning in children. Rats fed a standard diet and poisoned

during a period of three weeks to 24 months fail to show any conspicuous liver injury. However, Chiodi and Cardeza produced severe liver damage in rats forcibly fed at a high fat diet. Death followed within six to 19 days, and the livers showed cellular and nuclear hypertrophy, fatty infiltration or degeneration and necrosis. Addition of choline, inositol, tocopherol and brewers' yeast prevented fatty infiltration or degeneration in most animals but not cellular and nuclear hypertrophy and necrosis. Casein and, to a lesser degree, methionine prevented cellular and nuclear hypertrophy and necrosis of the liver when added to the high fat diet with lipotrophic agents in the presence or absence of yeast. Casein prevented the death of the animals poisoned with lead and fed the high fat diet within the experimental period only when yeast was also present in the diet.

CHAN, San Francisco.

RENAL EXCRETION OF WATER AND ANTI-DIURETIC SUBSTANCES IN PATIENTS WITH HEPATIC CIRRHOSIS AND RATS WITH DIETARY LIVER INJURY. CHARLES A. HALL, BOY FRAME and VICTOR A. DRILL, Endocrinology **44**:76 (Jan.) 1949.

Extracts of urine from patients with hepatic cirrhosis and ascites had antidiuretic activity when assayed on rats, whereas similar extracts of urine from normal subjects were devoid of such activity.

JACOBSEN, Buffalo.

LYE BURNS OF THE ESOPHAGUS. BAILEY WEBB and DORIS SURLES WOOLSEY, J. A. M. A. **141**:384 (Oct. 8) 1949.

Experiences in treating 39 lye-burned children are discussed. All patients who have given a history of ingesting lye should be admitted to the hospital, and if there is evidence of burn in the mouth laryngoscopy and esophagoscopy should be done. A thick barium sulfate preparation is a better diagnostic medium than a thin one. Early dilation from above is not so painful as gastrostomy and retrograde dilation. In the cases reported by Webb and Woolsey, a physician saw each of 31 of the 39 patients within 48 hours after ingestion. In most instances, local treatment to the mouth only was, unfortunately, prescribed.

KIMBALL, Evanston, Ill.

FIBROSIS OF THE PANCREAS IN INFANTS AND CHILDREN. CHARLES D. MAY and CHARLES UPTON LOWE, J. Pediat. **34**:663 (June) 1949.

The symptoms of cystic fibrosis of the pancreas are the effects of an interplay of changes in the pancreas and the lungs. They vary considerably in different patients, and May and Lowe decry the tendency to segregate patients with this disease into "types." The disease is hereditary, a mendelian recessive characteristic. It appears just before, at, or shortly after birth and progresses rapidly. Although meconium ileus is not necessarily an associated symptom, it may be the first sign of cystic fibrosis. By the end of the fourth week, two thirds of the patients will have begun to exhibit symptoms. These symptoms may be referable to the feces or the lungs. The most dependable sign in the feces is increased bulk and weight over a period of time. Most patients preserve a good appetite, and if pulmonary complications do not intervene fairly normal nutrition may be maintained.

Pulmonary changes vary. In the mildest form there is peribronchial infiltration and emphysema. In severer cases there is a mucopurulent viscid bronchial and bronchiolar exudate. Alveolar consolidation, bronchiolectases and scattered small abscesses may be encountered. The bronchiolar obstruction produces emphysema and atelectasis. Infection with Staphylococcus aureus is regularly present. Sometimes the physical signs of these changes may not be prominent, and in such cases roentgenograms of the chest may be valuable. As a result of these pulmonary changes the authors have seen cardiac dilatation and hypertrophy. With hypertrophy they have seen signs of cardiac failure, edema and ascites that could not be explained on a nutritional basis.

Aerosol antibiotics are valuable in the control of pulmonary infection. The pulmonary changes reach their maximum intensity and then tend to subside. Children who have lived to 5 to 8 years may be almost free of pulmonary complaints. The pancreatic changes are

irreversible, and intestinal symptoms will persist. However, the intestines are extremely adaptable and absorption of fat and protein may be 60 per cent or more of normal, despite the absence of pancreatic enzymes.

The authors suggest use of a well balanced diet in this disease. Three times the usual intake of vitamins A and D should be given by the oral route. Pancreatin is of doubtful value.

MACDONALD, Pittsburgh.

ROENTGEN MANIFESTATION OF INFANTILE HYPERTROPHIC PYLORIC STENOSIS. HERBERT OLNICK and H. STEPHEN WEENS, J. Pediat. **34**:720 (June) 1949.

Gastric hyperperistalsis, dilatation and retention may be seen in roentgen studies of hypertrophic pyloric stenosis, but these signs are not specific for this disorder. In most cases of pyloric stenosis, a narrowing and stiffening of the stenotic canal can be demonstrated roentgenologically and is a pathognomonic sign. In addition, many cases of pyloric stenosis will show indentation of the duodenal cap; this distortion of the pyloric segment of the stomach may persist for years after operation without producing symptoms.

MACDONALD, Pittsburgh.

MECONIUM ILEUS. WALLACE SAKS, New Orleans M. & S. J. **102**:75 (Aug.) 1949.

Meconium ileus is a result of pancreatic achylia present at birth. If pancreatic achylia occurs between birth and 1 year of age, the picture is that of cystic fibrosis of the pancreas with pulmonary changes or cirrhosis of the liver. After one year the picture resembles that of idiopathic celiac disease.

Progress has been made in relieving the obstructive meconium, but the patient invariably dies of pancreatic achylia.

MCGUIGAN, Evanston, Ill.

SECRETIN TESTS WITH BILUMEN GASTRODUODENAL DRAINAGE IN INFANTS AND CHILDREN. GORDON E. GIBBS, Pediatrics **5**:941 (June) 1950.

Construction and use of a bilumen gastroduodenal tube for infants are illustrated and discussed. Secretin tests were performed on 12 normal infants and children, 11 with cystic fibrosis of the pancreas, two with celiac disease and one each with lipid pneumonia and Salmonella enteritis.

In control patients, secretin produced an approximately fourfold increase of the 20 minute volume of flow and an increase of the p_H and titrable alkalinity. Amylase and trypsin decreased in concentration but increased in total quantity per unit time.

Bilumen gastroduodenal drainage is practical in the small infant. Employment of this and secretion together is believed to increase the reliability of duodenal drainage without adding significantly to the difficulty of the procedure.

FROM THE AUTHOR'S SUMMARY.

THE TINCTORAL DEMONSTRATION OF A GLYCOPROTEIN IN WHIPPLE'S DISEASE. B. BLACK-SCHAFFER, Proc. Soc. Exper. Biol. & Med. **72**:225 (Oct.) 1949.

The etiology and pathogenesis of Whipple's disease (intestinal lipodystrophy), a clinical syndrome similar to sprue, is not known. The disease may be recognized anatomically by nonlipid macrophagocytosis in the lamina propria of the small intestine and occasionally the proximal colon, lipogranulomatosis of the mesenteric lymph nodes and absence of chylous obstruction and clinically by poor absorption of fat, glucose and probably protein and the absence of macrocytic anemia. Sections of intestines from four patients were treated with Schiff's periodic acid stain which revealed that the phagocytosed material in the mucosa stained deep scarlet. Lymph nodes of three patients revealed that many macrophages stained a brilliant scarlet. The periodic stain depends on oxidation of a 1-2 glycol bond in a polysaccharide, forming polyaldehydes, which therefore take up the fuchsin of Fuelgin's reagent. The polysaccharide is insoluble in water and the reaction to mucicarmine stain indicates it is bound to protein—thus is a glycoprotein. Black-Schaffer suggests the eponym Whipple's disease be used until the true nature of the disease is determined.

HANSEN, Galveston, Texas.

CALCIFICATION IN SYMPATHOBLASTOMA (NEUROBLASTOMA). F. B. MANDEVILLE, Radiology **53**:403 (Sept.) 1949.

A tumor containing numerous calcifications in the left hypochondrium of a child aged 2 years is described and illustrated by three roentgenograms. Emphasis is laid on the likelihood of sympathoblastoma in tumors of young children that show calcifications, although calcification is not considered pathognomonic of this or any other tumor.

ANSPACH, Chicago.

CONGENITAL REDUPLICATION OF THE ESOPHAGUS. RALPH C. FRANK and LESTER W. PAUL, Radiology **53**:417 (Sept.) 1949.

A 5 year old boy complained of particles of food becoming lodged in his throat. The food would not descend, nor could it be regurgitated. Incidents of this kind occurred only occasionally after the child was taught to chew his food well and drink large quantities of water. A gastrointestinal examination at the age of 10 years revealed a bifurcation of the esophagus for a distance of 13 cm. The barium sulfate outlined both channels, one of which was larger than the other. They reunited just above the diaphragm and entered the stomach as a single tube. A return examination seven years later revealed that both channels of the esophagus were still functioning but that one was considerably larger than the other at this time.

This case is reported because of the rarity of cases of this kind.

ANSPACH, Chicago.

INFECTIOUS DIARRHOEA OF INFANCY. H. W. PRICE, Canad. M. A. J. **62**:351 (April) 1950.

A survey of 500 cases of infectious diarrhea indicated that the decline in incidence and mortality is partially due to forces beyond the control of the medical profession. Chemotherapy has helped but little, and the true nature of the condition is still not understood. The outstanding contribution of scientific medicine has been the replacement of fluids and electrolytes and the combating of shock.

McGUIGAN, Evanston, Ill.

DUPLICATION OF THE RECTUM. C. O. F. RIEGER, Clin. Rep. Adelaide Children's Hosp. **1**:242 (Nov.) 1949.

A case of duplication of the rectum is discussed, and the subject is briefly reviewed.

McGUIGAN, Evanston, Ill.

HIRSCHSPRUNG'S DISEASE AND IDIOPATHIC MEGACOLON. DENIS H. THOMPSON and JOSE KAY, South African M. J. **24**:73 (Feb. 4) 1950.

The recent advances in the treatment of Hirschsprung's disease (congenital megacolon) are discussed, and the differences between this and idiopathic megacolon are pointed out. Case reports are included.

McGUIGAN, Evanston, Ill.

REPAIR OF CONGENITAL ATRESIA OF THE OESOPHAGUS. J. W. ROBERTS, South African M. J. **24**:167 (March 11) 1950.

The problem of congenital atresia of the esophagus is discussed from the anesthetist's viewpoint. The author believes from his experience in 8 cases that general anesthesia must be used and that cyclopropane is the agent of choice. Curare and controlled respiration are important adjuncts.

McGUIGAN, Evanston, Ill.

INFANTILE HEPATIC CIRRHOSIS. S. S. MISRA, J. Indian M. A. **19**:126 (Jan.) 1950.

A brief summary of present knowledge of infantile hepatic cirrhosis is given. The cause is not known. Treatment is generally supportive, with attention to diet, correction of anemia and eradication of infection.

McGUIGAN, Evanston, Ill.

AN UNUSUAL CASE OF HEPATIC DYSPLASIA WITH TELANGIECTASIS AND HYPEREMIA IN AN INFANT. M. OLANDELLI and M. A. DINA, Clin. Pediat. **31**:239 (April) 1949.

The mother of the infant discussed had primary melanosarcoma on the right side of her forehead, with multiple metastases.

The infant was dystrophic from birth and died at the age of six months. At autopsy, the striking pathological changes were in the liver in which there were edema, telangiectasia, hyperemia, dilatation of the sinusoids and generalized cellular atrophy.

HIGGINS, Boston.

STREPTOMYCIN IN THE TREATMENT OF ENTERITIS IN INFANTS. R. BULGARELLI and P. TOLENTINO, Policlin. inf. **16**:608 (Dec.) 1948.

Forty-six infants with enteritis were treated with streptomycin. Only one of the 33 cases in which the streptomycin was taken by mouth (100 mg. per Kg. per day in four doses) was regarded as a therapeutic failure. On the other hand, only eight of 13 cases in which the streptomycin was given intramuscularly, and two of five cases in which the administration was by rectum were therapeutic successes.

Rectal administration is recommended only in cases of colitis, and intramuscular administration, only in cases of septicemia.

Streptomycin was regarded of special value in the cases of parenteral diarrhea in which the intestinal flora had secondarily become virulent.

HIGGINS, Boston.

A CASE OF NOMA WITH RECOVERY. N. CARRARA, Policlin. inf. **16**:599 (Dec.) 1948.

After a severe typhoid infection, a girl of 4½ years had gangrenous stomatitis. Excellent recovery followed intensive therapy, which included blood transfusions, roentgen therapy and administration of neoarsphenamine and antigangrene serum. Special credit for the recovery is ascribed to the patient's having received large doses of vitamins A and C.

HIGGINS, Boston.

ACTION OF AN ASSOCIATED FORMOSULFAMIDE IN ENTERITIS OF CHILDREN. A. LEONE, Lattante **21**:156 (March) 1950.

Methylsulfathiazole, also called formosulfathiazole, proved efficacious in the treatment of bacillary dysentery. This drug was used in 18 cases; 13 children showed rapid recovery, four showed some improvement and one died. The theory is advanced that the drug breaks down to form a formaldehyde molecule, affording additional antibiotic action to that from the sulfathiazole.

HIGGINS, Boston.

CONGENITAL ANOMALIES AS FACTORS IN DISORDERS OF THE PYLORIC PASSAGE. EVA FARKAS. Ann. paediat. **174**:385 (June) 1950.

Strangulation of the pyloric passage can resemble in clinical manifestations the real pyloric stenosis. Owing to the imperfect absorption of the mesenterium ventricle, irregular peritoneal bundles may develop as its rudiments. Of similar origin is the ligamentum cystogastrocolicum, which is not a single ligament, but a bundle consisting of fibers spreading out in a fan shape. This pseudoligament is able to strangulate the pyloric region and imitate symptoms similar to those of pyloric stenosis. Projectile vomiting sets in at a later stage. Visible peristalsis, palpable tumor and the "pyloric" facial expression are missing. Vomiting occurs in the cycles. Consequently, the general condition does not deteriorate rapidly. It can be improved by operative means only.

FROM THE AUTHOR'S SUMMARY.

THE IMPORTANCE OF EARLY DIAGNOSIS AND TREATMENT OF A SHORT ESOPHAGUS. A. DE MAESTRI and G. CORRADI, Minerva Pediat. **2**:41 (Jan.) 1950.

Two cases are reported of a congenitally short esophagus with herniation of the stomach through the diaphragm. In one child, the diagnosis was made by roentgenography at the age of 4 months, 20 days after the onset of symptoms of vomiting; often bloody, tarry stools and

loss of weight. Peristalsis had not been observed, and atropine had been of no benefit. Treatment consisted in the giving of a thicker food and in maintaining the child in an upright position after feeding. At the age of 26 months, he is developing normally and has vomiting spells only with intercurrent infections.

The other child was 9 years old before the diagnosis was established. Because of stenosis of the lower part of the esophagus and ulceration of the mucosa, surgical resection was necessary. Some anemia still persists; a little blood persists in the gastric juice and the stools react positively to guaiac tests. The boy's general condition, however, is improving.

HIGGINS, Boston.

APPENDICITIS FROM OXYURIS. E. DOGNINI and G. C. ABBA, Minerva Pediat. **2**:49 (Jan.) 1950.

Of 142 patients operated on for appendicitis at the Children's Hospital of Brescia, pinworms were found in the lumen of the appendix of 19 (13 per cent). No preoperative clinical diagnostic signs differentiated the appendicitis due to the pinworms. Therefore, surgical treatment is imperative regardless of the cause.

HIGGINS, Boston.

INTUSSUSCEPTION IN THE INFANT. EMILIO ROVIRALTA, Acta pediat. españ. **85**:1 (Jan.) 1950.

Roviralta believes that surgical treatment is not always necessary in case of intussusception. He points out that many invaginations would reduce themselves and that the words "operation with cure" have been used in cases in which no serious invagination or intussusception existed. In the first place, the probability of a reduction without surgery is in inverse proportion to the grade of constriction and in most cases is entirely independent of the time that the symptoms have existed. Secondly, the fear of perforation if a reduction by way of enemas is attempted is certainly no more serious than the surgical removal of the necrotic portion of an intestine. In both instances there are always the antibiotics to combat infection.

The author includes roentgen studies and reports of cases with reduction by opaque enemas. The results were good on one patient when this technic was employed five days after the beginning of the syndrome.

The author compares the statistics of Ladd and Gross, of the Boston Children's Hospital, with those of Hellmer, of Switzerland. Ladd and Gross operated on 88 infants, with no deaths in the first 24 hours, 18 per cent mortality from 24 to 36 hours and 50 per cent mortality after 48 hours. Hellmer, with the conservation method, treated 162 patients and had a 2 per cent mortality among the patients treated within 12 hours; no deaths among those treated in the 12 to 24 hour period, 10 per cent among those treated in the 24 to 48 hour period and 31 per cent among those treated after 48 hours.

After the enema the child is given fluids, and if he goes to sleep it is almost certain the reduction has taken place. Pouliquen advises a second enema before resorting to surgical intervention.

The only patient whom Roviralta has lost with his conservative treatment was a child brought in in shock. Plasma was given, but the child did not recover sufficiently for operation. Autopsy did not show any necrosis of the invaginated area.

In his discussion of the literature the author mentions the time limit, which has been stated in many different countries to be quite different. This would be inexplicable if there were not some factors other than the time element.

MARY ALLEN, Santa Fe, N. Mex.

HYPOCALCEMIA AFTER DIARRHOEA. C. SMEENK, Maandschr. v. kindergeneesk. **17**:355, 1950.

Smeenk presents descriptions of 6 children with symptoms of hypocalcemia following diarrhea. The symptoms were edema, hemorrhages, paralytic ileus, convulsions and carpopedal spasms.

FROM THE AUTHOR'S SUMMARY.

Diseases of Genitourinary Tract

MICROCYSTIC (THYROID-LIKE) KIDNEY. H. W. VOTH, Arch. Path. **47**:293 (March) 1949.

What is considered by the author to be a form of congenital cystic kidney, namely, microcystic thyroid-like kidney, is described here in a report of a case of a 22 year old Negro woman dying in uremia. Both of her kidneys appeared normal in size and grossly exhibited

none of the appearance of chronic pyelonephritis. The cut surfaces of the kidneys resembled those of a diffuse colloid goiter, the appearance caused by cystic enlargement of tubules filled with albuminous material in the cortex and medulla. Usually such dilatation of renal tubules is regarded as a result of chronic pyelonephritis in the medulla in which a productive inflammation causes fibrosis of the pyramids. This fibrosis forms a barrier near the corticomedullary junction, resulting then in obstruction to the tubules and the consequent appearance of "thyroid-like" cystic dilatation. Inflammatory cells were present in both cortex and medulla of the kidneys in the case reported, but the inflammation did not appear to interfere with the continuity of the tubules and the pelvis. The author interprets this finding as a secondary interstitial nephritis, a not uncommon complication of congenital cystic kidney.

HAW CHAN, San Francisco.

THE EFFECT OF ADRENALECTOMY ON THE RENAL TUBULAR REABSORPTION OF WATER IN THE RAT. WILLIAM D. LOTSPEICH, Endocrinology **44**:314 (April) 1949.

It is well known that the adrenal-insufficient animal excretes a given dose of water at a slower rate than the normal animal. In this paper there are presented data which indicate that the basis for this deficiency in water excretion is an increased resorption of water by the renal tubules in the absence of the adrenal cortex hormones.

JACOBSEN, Buffalo.

CARCINOMA OF THE CERVIX IN THE FIRST YEAR OF LIFE; REPORT OF TWO CASES. GEORGE P. HECKEL, Pediatrics **5**:924 (June) 1950.

Two cases of adenocarcinoma of the cervix in girls 7 and 11 months old are described. The first died of the disease on the day of admission to the hospital, having had vaginal bleeding for about a month. The second is surviving normally 20 months after total hysterectomy, leaving the ovaries undisturbed. Vaginal bleeding had begun eight days before admission.

There is probably but one previously reported case of such a carcinoma in a patient under 1 year of age. This tumor, too, was an adenocarcinoma. Reports of this case by different authors have led to the impression that there were two such cases.

FROM THE AUTHOR'S SUMMARY.

ANTHISAN IN THE TREATMENT OF ACUTE NEPHRITIS. T. R. THOMSON, Clin. Rep. Adelaide Children's Hosp. **1**:257 (Nov.) 1949.

Seventeen patients with acute nephritis were treated with "anthisan," an antihistaminic. No significant effect on the disease was noted.

MCGUIGAN, Evanston, Ill.

Nervous Diseases

MESANTOIN IN THE TREATMENT OF EPILEPSY. HARRY L. KOZOL, Arch. Neurol. & Psychiat. **63**:235 (Feb.) 1950.

Results in 200 patients treated with mesantoin® (methylphenylethel hydantoin) over periods of two months to four years are analyzed. One hundred and thirty-two were greatly improved, attacks reduced in frequency to one fourth; 43 were improved, attacks reduced to nearly one fourth and intervals between attacks nearly doubled. Kozol states the belief that mesantoin® is one of the most effective drugs yet developed. Toxicity is low. It is more effective than any other anticonvulsant drug in cases of epilepsy secondary to cerebral trauma. Nine of 10 patients with psychomotor seizures were greatly improved.

MCGUIGAN, Evanston, Ill.

HEREDITARY ATAXIA; CLINICAL STUDY THROUGH SIX GENERATIONS. JOHN W. SCHUT, Arch. Neurol. & Psychiat. **63**:535 (April) 1950.

Over six generations of one family, 45 persons, exhibited hereditary ataxia. Conditions out of a total of 342 members of the family were found which could be classified as Frederick's ataxia, hereditary cerebellar ataxia and hereditary spastic paraplegia. The age of onset varied from 17 to 35 years, with an average of 26.5 years. The age of onset in each succeeding generation was two to four years earlier.

MCGUIGAN, Evanston, Ill.

OSTEOBLASTIC MENINGIOMA IN A CHILD. LEO MADOW and R. A. FARMER, Arch. Neurol. & Psychiat. **63**:596 (April) 1950.

A case of osteoblastic meningioma in a child of 12 years is reported. Symptoms had begun at the age of 4 years.

McGUIGAN, Evanston, Ill.

ALLERGIC EPILEPSY. W. AMBROSE McGEE, New Orleans M. & S. J. **101**:601 (June) 1949.

The author notes 6 cases which show a possible relation between allergy and epilepsy. All the patients were treated before the age of electroencephalography. Recently it has been shown that a high percentage of allergic children show electroencephalographic abnormalities regardless of whether the allergy is complicated by behavior problems or seizures. Three of the author's 6 patients showed favorable responses to allergic therapy.

McGUIGAN, Evanston, Ill.

SUBDURAL HEMATOMAS AND FINDINGS FROM OBSTETRICAL TRAUMA. I. J. JACKSON and A. WERNER, Helvet. paediat. acta **5**:59 (March) 1950.

1. Subdural hematomas due to birth injury can be classified in two groups: acute, with immediate, severe clinical syndrome, and chronic, with late syndrome.

2. The clinical picture in the acute cases shows mostly a skull fracture with signs of brain lesion: convulsions, hemiparesis and stiffness of the extremities.

The clinical picture in the chronic cases shows generally as an outstanding feature a progressive hydrocephalus with epileptic seizure, abnormal neurologic signs and a bad state of nutrition. (Some cases of microcephaly should belong to this group.)

3. The clinical history and the objective findings generally allow the tentative diagnosis. The definite diagnosis can be made only by finding the fluid through the burr hole or by direct puncture through the fontanel.

4. In the authors' opinion, the treatment aims not only at removal of the space-occupying fluid collection but at removal also of the membrane which prevents the brain from extending normally. The dietetic measures form an important part of the treatment, to restore and maintain the caloric intake and the fluid balance. This is especially important if the patients have to undergo a long and tiring procedure.

The authors agree with Elvidge and Jackson that the problem of subdural hematomas and effusions due to birth injury concerns three specialists: the obstetrician, to avert them; the pediatrician, to discover them early enough, and the neurosurgeon, to treat them. It also concerns a fourth specialist too often forgotten, the family doctor.

FROM THE AUTHORS' SUMMARY.

FAMILIAL SALAAM CONVULSIONS. HANS ZELLWEGER and RUDOLF HESS, Helvet. paediat. acta **5**:85 (March) 1950.

The case histories of 5 children who belonged to two different families are given. These children all had either salaam convulsions or myoclonic jerks (*Blitzkrämpfe*). The first 3 children were boys and were the offspring of a consanguineous marriage; they had 3 healthy sisters. The convulsions began during the first year of life and resulted in complete idiocy in the 2 older boys. The pneumoencephalogram revealed the presence of hydroencephalus in all 3 boys, and 1 of them, in addition, had shown a hypertrophied and calcified choroid plexus; in 1 of the others a cavum Vergae (vergas ventricle) was revealed. The electroencephalogram indicated localized right-sided epileptic potentials in the frontotemporal region; in 1 of the other patients generalized epileptic potentials were present. The other cases concern 2 sisters (but in this instance the parents' marriage was not consanguineous) who suffered from idiopathic convulsions of the following types: myoclonic jerks, spasmus nictitans and salaam convulsions. This is the first recorded observation of the familial occurrence of these three forms of convulsions.

FROM THE AUTHORS' SUMMARY.

Psychology and Psychiatry

PERSONALITY CHARACTERISTICS AND EMOTIONAL PROBLEMS IN STUTTERERS UNDER THE AGE OF FIVE. PHILIP J. GLASNER, J. Speech & Hearing Disorders **14**:135 (June) 1949.

Seventy stutterers under 5 years, studied relative to their emotional and social maladjustments, were divided into three main types: a healthy, aggressive type of child, with emotional pampering and criticism from a relative suddenly coming into the family; an ungainly, awkward type, with brilliant parents and a whole constellation of emotional disturbances because of hostility from one parent or the other, and a dependent, confused and fearful type. The author states that children of this type have a long background of overprotection and pampering and overanxious, excessively perfectionistic parents.

PALMER, Wichita, Kan. [ARCH. OTOLARYNG.].

POST TRAUMATIC NEUROSIS. RAYMOND T. BINNS, Clin. Rep. Adelaide Children's Hosp. **1**:270 (Nov.) 1949.

Profound manic-depressive emotional disturbance following a head injury is described. Recovery was gradual over a period of ten months.

McGUIGAN, Evanston, Ill.

Diseases of Ductless Glands; Endocrinology

THE ADMINISTRATION OF ADRENOCORTICOTROPHIC HORMONE TO NORMAL HUMAN SUBJECTS: THE EFFECT ON THE LEUCOCYTES IN THE BLOOD AND ON CIRCULATING ANTIBODY LEVELS. PHILIPPA H. HERBERT and JOAN A. DE VRIES, Endocrinology **44**:259 (March) 1949.

Circulating antibody levels in normal human subjects were not increased after the administration of large quantities of adrenocorticotropic hormone. The findings of other workers regarding blood eosinophil and lymphocyte counts have, however, been confirmed. Both types of cells showed diminished counts, the fall in eosinophils being more marked and of longer duration the larger the amount of hormone injected.

JACOBSEN, Buffalo.

A NEW PROCEDURE FOR THE DETERMINATION OF THE ANTIDIURETIC PRINCIPLE IN THE URINE. ARTHUR GROLLMAN and BETTY WOODS, Endocrinology **44**:409 (May) 1949.

It is generally accepted that the neurohypophysis secretes a hormone which plays an important role in the water economy of the organism. This antidiuretic hormone is presumably excreted in part in the urine, the antidiuretic activity of which has been found to parallel the need of the organism for the hormone. Thus, during dehydration resulting from forced abstinence from water or in various clinical conditions, the nephrotic stage of glomerulonephritis, eclampsia, the antidiuretic potency of the urine is enhanced considerably over normal. In dehydration, structural changes are also noted in the neurohypophysis, which are suggestive of increased activity of this tissue.

A new procedure is described for concentrating the antidiuretic principle of the urine based on adsorption on charcoal, elution by glacial acetic acid and precipitation by purified benzine and absolute alcohol. The method offers several advantages over previously available procedures.

JACOBSEN, Buffalo.

THE ANTIDIURETIC HORMONE IN THE URINE IN EXPERIMENTAL AND CLINICAL HYPERTENSION. MICHAEL E. ELLIS and ARTHUR GROLLMAN, Endocrinology **44**:415 (May) 1949.

Hypertension, experimentally induced in laboratory animals as well as the clinical form of this disorder, is accompanied with certain changes in salt and water metabolism. These observations suggested the desirability of a study of the excretion of the antidiuretic principle in the urine in various forms of hypertension in order to determine to what extent the altered salt and water metabolism in hypertension is accompanied with changes in the antidiuretic activity of the urine.

The present results demonstrate an increased excretion of antidiuretic principle in the urine of hypertensive patients and of dogs and rats with induced experimental renal hypertension.

JACOBSEN, Buffalo.

THE INFLUENCE OF ASCORBIC ACID ON THE ADRENAL WEIGHT DURING EXPOSURE TO COLD. LOUIS-PAUL DUGAL and MERCEDES THERIEN, Endocrinology **44**:420 (May) 1949.

It is well known that any type of stress produces an increase in weight of the adrenal glands, and it is believed that the weight response in such conditions is an aspect of the functional adaptation of the adrenal glands to the increased requirement for cortical hormones by the organism; in other words, that the gain in adrenal weight, under conditions of stress, is due to a hypertrophy of the cortex with a corresponding increase in production of adrenal cortex hormones and consequently an increased resistance toward the damaging agent. It has also been shown by many authors that the enlargement of the adrenal cortex can be prevented or, even more, that the gland may become atrophied when the animals under stress are treated with sufficiently high doses of adrenal cortex hormones. On the other hand, it has been reported often in recent years that a relation of some sort, still obscure, seems to exist between the ascorbic acid level of the adrenal cortex and the hormonal activity of the latter.

In this paper, the authors are able to show that the typical enlargement of the adrenal glands under the influence of stress, observed many times before by other workers and by themselves for their controls in this actual series of experiments in which cold was the damaging agent, is completely prevented in rats and guinea pigs exposed to cold if they receive large doses of ascorbic acid. Those experiments show that ascorbic acid seems to play a compensatory role somewhat similar to the one of adrenal cortex hormones. The normal hypertrophy is prevented—although there is no atrophy—but, at the same time, the resistance to cold is increased.

JACOBSEN, Buffalo.

THE RELATIVE GROWTH OF THE THYROID GLAND IN THE BOVINE FETUS: THE ACCUMULATION OF THYROXINE-LIKE AND OTHER IODINE COMPOUNDS IN THE FETAL BOVINE THYROID. C. W. NICHOLS JR., I. L. CHAIKOFF and J. WOLFF, Endocrinology **44**:502 (June) 1949.

The nature of thyroid iodine in the postnatal state is fairly well understood. At least 90 per cent of it is organic, and almost all of this can be accounted for by two fractions: Thyroxine-like and diiodotyrosine-like iodine. These two compounds do not exist in the free state in the gland but are combined there with other amino acids to form the characteristic thyroid protein, thyroglobulin. The nature of the iodine in the fetal organism has not been clearly established. To obtain such information, a study of various iodine fractions of the bovine fetal thyroid gland was undertaken. It was found that thyroid weight in the fetus is nearly directly proportional to body weight.

The amounts of iodine found in the bovine fetal thyroid gland with increasing age were greater than could be accounted for by mere increase in thyroid mass. A progressive increase in the iodine-concentrating capacity of fetal thyroid tissue occurred with age.

JACOBSEN, Buffalo.

HISTOLOGICAL, CYTOCHEMICAL AND PHYSIOLOGICAL OBSERVATIONS ON THE REGENERATION OF THE RAT'S ADRENAL GLAND FOLLOWING ENUCLEATION. ROY O. GREEP and HELEN W. DEANE, Endocrinology **45**:42 (July) 1949.

With the accumulation of evidence for a functional zonation of the adrenal cortex, the origin and functional capacity of new cortical tissue arising after enucleation of the gland acquire new significance. Enucleation of the adrenal gland involves slicing open the capsule and extruding the medulla and most of the cortex. If both glands are so enucleated or if one gland is enucleated and the other totally removed, regeneration of cortical tissue takes place so rapidly that the original volume is restored in about a month. The regeneration is dependent on the presence of the pituitary gland.

The experiments here reported indicate that the regenerated cortex apparently secretes hormones governing both salt and sugar metabolism, and the normal functional zonation is restored.

JACOBSEN, Buffalo.

SEROLOGIC STUDIES ON CRYSTALLINE ADRENOCORTICOTROPHIC HORMONE: THE PRODUCTION OF ANTIADRENOCORTICOTROPHIN. JEANNE H. CHASE, Endocrinology **45**:96 (July) 1949.

In view of the widespread use of the adrenocorticotropic hormone, in both clinical and animal experimentation, the problem of the formation of a substance antagonistic to the action of this hormone is a pertinent one. It is here reported that a substance antagonistic to the normal action of the adrenocorticotropic hormone has been demonstrated in the serums of mice treated by increasing daily doses of pure adrenocorticotropic hormone over a period of 25 days.

JACOBSEN, Buffalo.

PRECOCIOUS PUBERTY. LYMAN W. MASON, J. Pediat. **34**:730 (June) 1949.

Precocious puberty in girls is usually that and nothing more. These girls show advanced bone age and, because of early closure of the epiphyses, are usually of short stature. Such children should have a pelvic examination under anesthesia, but surgery is not indicated unless palpable evidence is found to justify it. Premature sexual development is rarely caused by granulosa cell tumor of the ovary. Heterosexual changes are found with tumors of other endocrine glands. Brain lesions with sexual changes are also accompanied with other system changes that should facilitate differentiation.

Precocious puberty should be treated with psychotherapy aimed at parents and child.

MACDONALD, Pittsburgh.

DEGENERATIVE CHANGES IN YOUNG DIABETIC PATIENTS IN RELATIONSHIP TO LEVEL OF CONTROL. H. L. JACKSON, R. C. HARDIN, G. L. WALKER, A. B. HENDRICKS and HELEN G. KELLY, Pediatrics **5**:959 (June) 1950.

The level of control, as well as the duration of the disease, is an important factor influencing degenerative changes, and good control will delay and possibly prevent such changes. Present knowledge makes it not only possible but practicable to maintain a high level of control of diabetes in children living in a well adjusted home. Until more knowledge concerning the treatment of childhood diabetes is available, a high level of control appears to offer the best means of averting or delaying chronic degenerative changes.

Additional knowledge is needed to understand the pathological physiology of various levels of noncontrol. An optimistic rather than a pessimistic outlook is warranted.

FROM THE AUTHORS' SUMMARY.

IDIOPATHIC HYPOPARATHYROIDISM WITH PAPILLEDEMA IN A BOY SIX YEARS OF AGE; REPORT OF A CASE ASSOCIATED WITH MONILIASIS AND THE CELIAC SYNDROME AND A BRIEF REVIEW OF THE LITERATURE. C. COLLINS-WILLIAMS, Pediatrics **5**:998 (June) 1950.

The case of a boy with idiopathic hypoparathyroidism, moniliasis and the celiac syndrome is reported. Moniliasis developed at the age of 16 months and was apparently cured promptly, but evidence of Candida albicans infection was found at several subsequent visits. At the age of 5 years, the boy began to have loose stools and at the age of 5 years 10 months a diagnosis of the celiac syndrome was made.

At the age of 6½ years he entered the hospital in severe tetany and was found to have hypoparathyroidism. His bones appeared normal on roentgenograms, and no intracranial calcification was observed. While he was in the hospital, bilateral papilledema developed and then receded, apparently in response to therapy for the hypoparathyroidism. Treatment consisted in administration of calcium gluconate, water-soluble vitamin D dihydrotachysterol and aluminum hydroxide gel by mouth and use of a high protein, low fat, low phosphorus diet. The stools became normal shortly after this diet was started.

Brief reference is made to his brother, in whom moniliasis developed at the age of 1 year 7 months, and the celiac syndrome appeared when he was about 3 years old. At 9 years of age he still has no evidence of hypoparathyroidism. The four other siblings are well.

The 22 previously reported cases of papilledema associated with hypoparathyroidism and the seven previously reported cases of moniliasis associated with hypoparathyroidism are briefly reviewed.

FROM THE AUTHOR'S SUMMARY.

DIABETES MELLITUS AND PREGNANCY. E. WYNNE-JONES, South African M. J. **23**:654 (July 30) 1949.

Observations in 20 cases of pregnancy in diabetic mothers are tabulated and analyzed. There were eight stillbirths and two neonatal deaths. Theories as to the cause of the continued high fetal mortality are discussed. The author advocates treating all babies as premature for the first two days, with use of an incubator and continuous administration of oxygen. Ten cubic centimeters of 10 per cent dextrose should be given every two hours for the first forty-eight hours. Routine induction of labor about four weeks before term is advised.

McGUIGAN, Evanston, Ill.

Diseases of Muscles, Bones, Joints and Lymph Nodes

LESIONS OF THE SPINAL CORD (TRANSVERSE MYELOPATHY) IN ACHONDROPLASIA. ALFRED VOGL and RAYMOND C. OSBORNE, Arch. Neurol. & Psychiat. **61**:644 (June) 1949.

Lesions of the spinal cord are not uncommon in achondroplastic adults, due in part to a congenital narrowness of the spinal canal, which barely accommodates the cord. Dorsolumbar kyphosis due to a wedge-shaped deformity of one of the vertebrae, typical of the achondroplastic spine, predisposes to localized osteoarthritis, with resulting compression of the vessels and nerve roots and consequent progressive paraplegia. This syndrome could be largely averted by institution of orthopedic measures before the achondroplastic infant assumes the upright position. Treatment by laminectomy if done early gives excellent results.

McGUIGAN, Evanston, Ill.

THE INCIDENCE OF CONGENITAL DISLOCATION OF THE HIP AT ISLAND LAKE, MANITOBA. CAMERON CORRIGAN and SIDNEY SEGAL, Canad. M. A. J. **62**:535 (June) 1950.

The authors noticed a strikingly large number of cripples among a group of 1,253 Indians living in an isolated community with considerable inbreeding. Forty-five persons with dislocation of a hip were directly observed, with evidence showing that other persons, not examined, would bring the total to 71, an incidence of 6 per cent. Genealogical studies showed that every one of the persons known or suspected to have the condition were connected by blood relationship. Presumptive evidence suggests that the primary cause of the condition described is hereditary.

McGUIGAN, Evanston, Ill.

IS PENICILLIN LESS EFFECTIVE IN OSTEOMYELITIS IN CHILDREN THAN IN ADULTS? R. JÅFS, Nord. med. (Finska läk.-sällsk. handl.) **36**:2093 (Oct. 17) 1947.

Six adults suffering from localized osteomyelitis were successfully treated with intramuscular injections of penicillin (total dose: 500,000 to 1,360,000 international units during five to thirteen days). Nine children aged 4 to 14 with the same type of disease were treated for four to fifty-six days with penicillin intramuscularly (total dose: 500,000 to 2,300,000). In only two cases did healing without sequestration occur; in the other seven operations had to be performed. Jåfs recommends intensified penicillin treatment combined with sulfonamide drugs for children.

WALLGREN, Stockholm, Sweden.

Cutaneous Diseases; Allergy

ACANTHOSIS NIGRICANS: REVIEW OF LITERATURE WITH RECORD OF A CASE. HASSAN SEIF EL-NASR and MOHAMMED EL-ZAWAHRY, J. Roy. Egyptian M. A. **33**:81, 1950.

The literature is briefly reviewed and a new case presented.

McGUIGAN, Evanston, Ill.

ALLERGY IN THE NEWBORN. H. LEHNDORFF, Ann. pædiat. **174**:194 (March) 1950.

In a newborn child during the first week of life a number of clinical signs can be observed, all of them transient and not interfering with its well-being. These phenomena are: erythema neonatorum, generalized lymph node swelling, enlarged spleen, edema, fever and eosinophilia; they represent the well known picture of serum sickness. The serum with which a fetus comes into contact is its mother's serum. The following hypothesis is offered to explain the pathogenesis: During pregnancy the fetus becomes sensitized by substances transmitted from the mother via the placenta. During labor many placental villi are torn and a great amount of maternal serum is pushed into the child's circulation. This repeated serum injection into a sensitized organism will provoke allergic reactions after some days. The rarity of such manifestations can be explained by the fact that the fetus as well as the newborn is not able to produce antibodies in a sufficient amount; therefore, allergic reaction will often remain below the threshold of clinical evidence.

FROM THE AUTHOR'S SUMMARY.

ATYPICAL CASE OF ERYTHEMA EXSUDATIVUM MULTIFORME IN CHILDHOOD WITH THE PICTURE OF SEVERE DIPHTHERIA. L. CSÖKE and L. NEBENFÜHRER, Schweiz. med. Wchnschr. **80**:306 (March 25) 1950.

A 10 year old boy was admitted to the hospital with slight catarrhal symptoms, a body temperature of 38 C. (100.4 F.), pain in the mouth and tongue and difficulty in swallowing. A month previously he had a skin eruption with small vesicles on the palms, soles and prepuce. The conjunctivas were injected; the mucosa of the mouth was covered with superficial ulcerations. These superficial lesions and the lesions of the conjunctivas became more intense. The symptoms of laryngitis with hoarseness and signs of beginning stenosis were added. The temperature rose to 40 C. (104 F.). Diphtheria bacilli could not be demonstrated. The only skin lesions, small subcutaneous hemorrhages, were seen in the palms and soles. The severity of the laryngeal symptoms increased for about thirty-six hours, when all signs started to diminish slowly; recovery was complete. Comparisons are made with some cases reported in literature. The case is regarded as one of greatest rarity.

AMBERG, Rochester, Minn.

Miscellaneous

LOCALIZATION OF PENICILLIN IN VARIOUS VISCERA AFTER ITS ADMINISTRATION INTRAMUSCULARLY AND BY AEROSOL. G. F. CODURI, E. CLERICI and G. B. LEONARDELLI, Minerva pediat. 2:24 (Jan.) 1950.

Observations were made on guinea pigs as to the penicillin content in the lungs, liver, kidneys, blood, brain, bile and urine at various intervals after the drug had been administered by injection or by aerosol. Aerosol administration led to a higher concentration in the lungs than did intramuscular injection. When penicillin was administered with pectin, the concentration of the drug was higher in the liver and kidneys.

HIGGINS, Boston.

TEST OF COLLOID LABILITY WITH CONGO RED. E. HOLZKNECHT and A. BENCINI, Minerva pediat. **2**:28 (Jan.) 1950.

This congo red test, as described by Seitz, was applied to the serums of healthy children and of children with tuberculosis or rheumatic fever. The test is done with 12 test tubes containing varying amounts of hydrochloric acid (p_H 2.17 to 4.12); diluted serum and congo red are added in turn, and the tubes in which precipitation occurs are noted. This precipitation occurred in more acid solutions with the serums of tuberculous children and of children with rheumatic fever than with the serums of normal children.

HIGGINS, Boston.

Society Transactions

CHICAGO PEDIATRIC SOCIETY

Arthur F. Abt, M.D., President

Regular Meeting, Dec. 20, 1949

Infantile Eczema. Dr. A. Matheson.

A brief clinical description of infantile eczema is presented, and the impracticability of its etiologic classification is pointed out. The role of the various allergens in its causation is discussed, and the importance of foods in very early infancy, as well as inhalants and contactants in later infancy and childhood, is stressed. The skin test does not give conclusive results; a plea is made to continue such testing whenever possible, particularly in older children. A brief outline for the management of a case of infantile eczema is presented, with stress on the importance of treating the allergic child as well as the eczema. Because of the protean characteristics of eczema, with its spontaneous remissions and exacerbations, the advisability of conservatism in evaluation of beneficial results from a single drug is mentioned.

Finally, the fate of the infant with eczema is illustrated by a report of a continued study of 61 cases from private practice over a period of 15 years. The record of this study shows that in a tremendously high percentage of infants with eczema major allergies developed in later life. Only 11 per cent of this group escaped major allergies. The comparative results of skin testing on these infants and of retesting with use of the same allergens in later life are given.

The Incidence and Management of Eczema in the First Year of Life. Dr. Abraham B. Schwartz, Milwaukee.

Severe intractable eczema is the exception in a disease in which the norm is quite amenable to treatment. As in all diseases in which immunologic mechanisms operate, rudimentary forms of eczema occur in large numbers without typical manifestations of the disease. Not every case of eczema seen in infants parades in an orderly fashion from erythema to crusting.

Among 1,000 infants seen for monthly check-ups in the home or office, I found 295 with dermatitis of an eczema-like character. Of these, 241 responded readily after the first treatment instructions and had no recurrences during the first year. Fifty-three had recurrence during the first year necessitating additional treatment. Forty-five responded after the second set of instructions in the course of a few days or a few weeks. In only eight patients was the condition resistant beyond the first year of life. In three of these the condition has cleared up since infancy; in the other five there continue to be exacerbations.

The pediatrician who sees his patients at monthly intervals has it in his power to modify the environmental experiences which play so important a role in the severity of eczema manifestations.

Since the infant's food is quite restricted, diet changes may be made without elaborate allergic technics. The treatment instructions must take into consideration the polyvalent cause of the disease.

DISCUSSION OF PRECEDING CASES

Dr. I. M. Levin: Both authors are to be complimented on their fortitude in discussing eczema before a pediatric group. One factor to which attention should be directed is the too early feeding of a large variety of foods to young infants. In my locale I am old fashioned because I disapprove of a mixed cereal-like pablum, egg and banana diet at the age of 1 month and a meat, vegetable soup and fruit diet at the age of 2 months. At 6 months the infant is on an adult diet, never having had a chance to be an infant. It would seem that the Lord would have provided a full set of dentures at birth if He had felt we needed meat in early infancy.

The adoption of an aggressive attitude is necessary to counteract this weak and dangerous program of the younger pediatricians, general practitioners and disciples of commercial houses.

Hektoen and Welker long ago showed the antigenicity of egg proteins and their passage from mother to child. Cornbleet described the use of unsaturated fatty acids like maize oil in the treatment of seborrheic eczema. Finkelstein in his lectures in this country advocated protein milk feedings plus liberal amounts of vitamin B for eczematous infants.

In my own practice I like the use of evaporated milk long boiled in the unopened can and the gradual introduction of single cereals and vegetables plus synthetic vitamins D and C, with avoidance of fish oils and orange juice.

DR. A. ROSENBLUM: I have been engaged in a study of gastrointestinal allergy in infants during the past year. It has been observed in a series of more than 50 babies that about one third have shown eczema at some stage of their development. In most infants the eczema has been mild but in a few very severe. The intestinal symptoms are diarrhea, vomiting and colic, either singly or in varied combinations. These were often unhappy fretful babies. Other manifestations of allergy were often present. A high family incidence was noted, and in many of these infants asthma later developed. These were almost entirely food allergies, with cow's milk being the common offender. By proper management directed at reducing the allergic insult, the intestinal symptoms as well as the eczema were generally controlled.

DR. JESSE R. GERSTLEY: As I listened to these two interesting papers I could not help thinking of an analogy with pyloric stenosis. Thirty years ago in cases of vomiting pyloric stenosis was a frequent diagnosis. Then when a better technic was used in feeding a certain group of patients, pyloric stenosis was ruled out. Later, pylorospasm was recognized. Now what is left is the real pyloric stenosis. This also seems to be true of eczema. My observations are like those of Dr. Schwartz. The number of cases we diagnose now as real eczema is much less than formerly after we have ruled out those due to various external causes of dermatitis.

In view of the newer studies and knowledge we have of allergy, may I ask Dr. Matheson what proportion of eczema does he now believe due to allergy?

DR. A. MATHESON (closing): I wholeheartedly agree with the statement made by Dr. Levin regarding the danger of early introduction of a large variety of foods. There is no doubt that this has been greatly overdone and, to my mind, with no particular advantage. Such early introduction of solid foods is contraindicated in the allergic infant, and it may contribute to the higher incidence of allergic manifestations that we have seen in the past several years.

My own experience with the use of evaporated milk in milk-sensitive patients is that it is of little value. Evaporated milk even when boiled for two hours is still allergenic.

I take it for granted that when we speak of infantile allergic dermatitis we are referring to a certain clinical entity. From the prophylactic point of view it is of no advantage to attempt to distinguish among mild, moderate and severe allergic dermatitis, and in this respect I differ with Dr. Schwartz's statement. An infant may have a mild eczema at one time which may become severe overnight. Similarly, in the infant with mild eczema severe bronchial asthma may develop in the future. The fate in the 61 cases of infantile eczema had no relation to the mildness or severity of the infantile eczema.

I fail to see why the pediatrician has such an aversion to the skin test, which in itself is a simple procedure and no more time consuming than a blood count or similar laboratory procedure. Though the skin test is not diagnostic, it is helpful. I like to keep a record of limited skin tests done on the young infant for future reference.

It is easy to speak of environmental control but not so easy to carry it out unless the full cooperation of the mother is obtained. I know of no more effective way than to point out to her positive reactions to skin tests with environmental substances.

In reply to Dr. Gerstley I would say that approximately 60 to 70 per cent of infantile eczemas are on an allergic basis. About 15 per cent are seborrheic and the remainder are unclassified and of no definite known cause.

DR. A. B. SCHWARTZ, Milwaukee (closing): Someone asked about synthetic vitamin preparations. I use calciferol (drisdol®). One discussant asked about the relation of colic to eczema. My records show that there are a larger number of eczema cases among colicky babies than among the noncolicky group. However, in many colicky babies eczema does not develop. As to skin testing, on which Dr. Matheson has put great emphasis, my objection is the one previously raised by Cooke and Hill—the test results have little clinical validity.

Diabetes Mellitus in Patients Under One Year of Age. Dr. Alvah L. Newcomb, Winnetka; Dr. Harry Farrell (by invitation) and Dr. Albert Hand (by invitation).

Diabetes mellitus in infancy has been recognized since 1789. Other authors have reported a 0.5 per cent incidence considering all age groups. We have found six cases, or 3 per cent, in a total of 202 cases in children under the age of 13 years. The age of onset of the disease in these cases was 4½, 7, 10, 10¼, 10½ and 12 months, and the family history was positive in two cases.

The symptoms in order of frequency are listed:

	Per Cent
Fever	100
Pulmonary signs and symptoms	100
Accelerated respiration	80
Rales and signs of pneumonia	66
Anorexia, vomiting	66
Coma	50
Loss of weight	33

The high incidence of pulmonary signs and symptoms is not given prominence in the literature. The diagnosis of diabetes must be considered when respiratory signs or symptoms subside with fluid therapy and antibiotics but hyperpnea and coma persist.

The first three patients died. It is possible that all three patients might have recovered from the diabetic acidosis and infection had pencillin been available to supplement the insulin.

Adequate insulin must be prescribed, but severe hypoglycemia must be prevented, since our last patient almost died from insulin shock. In the third case apnea developed 2½ hours after the last recorded blood sugar level of 105 mg. per 100 cc.

DISCUSSION

Dr. Alvah L. Newcomb, Winnetka: When Dr. Farrell and I started to go through these cases we had no idea what we would find. We knew we had two recent cases in which the patients had been extremely ill with respiratory tract diseases and another in which the patient had not been so sick, but it seemed that penicillin was the thing that really saved these children, in addition to management with insulin and fluids. In the first case, in 1929, the patient would get along well for four or five days and then get the usual diarrheal disease that every child seemed to get in those early days, and he gradually went downhill and died. In the second case the blood sugar level dropped only to 470 mg. per 100 cc. but the child died; the temperature was 105 F. The last patient was treated during the war. The blood sugar was 105 mg. per 100 cc. 2½ hours before the child died, which I presume was due to hypoglycemia with anoxia of the respiratory center.

The principal reason for presenting this report is to call attention to the fact that one must consider diabetes in severe respiratory tract infections which fail to respond to the usual chemical, antibiotic and fluid therapy.

Dr. Jesse R. Gerstley: It would be interesting to know whether the atrophy in the pancreas was limited to the islands of Langerhans or was generalized. If the latter, were there symptoms or pathological findings suggestive of cystic fibrosis and generalized pancreatic insufficiency?

Dr. Phillip L. Aries: I directed an active diabetic service at the Cook County Children's Hospital for a number of years. During that time the youngest child having diabetes who came under my personal observation was 3 years old. The material presented by Drs. Newcomb, Farrell and Hand is important and impressive because of the early age of the infants when diabetes was recognized. It requires clinical acuity and an effort to obtain urine specimens for analysis to make the diagnosis in these cases. The symptomatology of an infection which goes on to produce an acidotic state merges so closely with the manifestations of diabetes that the clinical significance of what is happening is easily overlooked.

One must be conscious of the possibility of diabetes in an infant, rare indeed as that condition is, in order to give the child a chance to benefit from the spectacular results of insulin and penicillin therapy, as was demonstrated in the cases presented.

DR. ALVAH L. NEWCOMB, Winnetka (closing): There was gross atrophy, and in no case was there dilatation of the ducts of the pancreas. The diagnosis was not quickly made but was made by the residents after diligent search. Why there are five cases now I do not know, unless it is because there are more diabetics living nowadays and as the years go by more young diabetics will show up.

Arthur F. Abt, M.D., *President*

Regular Meeting, Jan. 17, 1950

The Management of Obesity in Childhood. MATTHEW M. STEINER.

Obesity in childhood is an expression of an imbalance between the intake of food and the output of energy and not the result of hormonal disturbance. Routine examination and investigation of the obese patient reveals an alert child of good stature with varying degrees and distribution of obesity, with no localizing endocrine or neurological findings and for whom laboratory investigations did not provide significant information. While not all obese children require specific therapy, there are many who, because of a basic disturbance in personality development, are, in addition, improved by a psychosomatic approach. The primary factors responsible for the imbalance between the intake of food and the output of energy in such cases can be attributed to the social and emotional problems of the child—the obesity is then considered as one overt expression of such difficulties.

As a result of maternal and familial hostility, anxiety or rejection, the initial growth and development of the child are distorted, and consequently, normal self expression and independence are stunted. Overdependence and overeating become weapons against stress and strain and often the only source of comfort in a hostile and puzzling environment. Suggestions have been made for the investigation of parent and child relationships both by physicians and by social agencies. In view of our position as pediatricians, opportunities for utilizing preventive methods in a long range program have been outlined in order that the tendency toward obesity during the critical stages in the life of the child may be interrupted.

While low caloric diets and anorexigenic drugs are helpful in some cases, the management of obesity requires, in addition, positive and constant family and child guidance. The criteria for management of the individual patient depend on the findings within the individual family unit.

The problems of the child and the family must be visualized and their solution attempted if we are to change the eating habits of the obese patient, encourage him to greater and more interesting activity and develop in him greater self confidence to cope with an ever changing and challenging environment.

DISCUSSION

DR. IWAN ROSENSTERN, Evanston: Endocrine obesity in childhood is rare. Simple obesity is more frequent. The latter may be permanent through childhood or temporary. The temporary type is by far the most common. It is prevalent in two age periods, infancy and puberty. It seems significant that these are the periods in which a larger deposit of subcutaneous fat is physiological. It seems of further interest that during the same periods a good, sometimes excessive, appetite and a large food intake are the rule. The obesity in infancy and puberty may be an exaggeration of physiological conditions. Most of the children who have transitory obesity at puberty are large in all their dimensions and exhibit a broad heavy skeletal frame. The boys usually have a fine skin and feminine features. Girls frequently show early maturation; boys show retarded sexual development (not alone the pseudoretardation due to an excessive amount of fat in the lower abdomen).

Longitudinal sections taken throughout childhood with serial measurements and photographs show that the development of obesity at puberty may start rather suddenly, within a period of a few months. They show furthermore that the obesity disappears after puberty without any treatment; it is a self limited disorder.

DR. WILLARD Z. KERMAN, Glencoe: Attendant to the current increased emphasis on psychogenic factors in various organic disorders, I would voice a word of caution in the matter of handling parents. It is a wise and basic psychiatric principle which cautions that no person be confronted with a psychodynamic formulation which he is emotionally unprepared

to accept. Such appraisals as "parental rejection," although readily apparent to an outsider, are usually unknown and unacceptable to the parent involved. To bluntly and callously confront him with such an observation, even though true, invites hostile, defensive reactions which serve only to impede the therapeutic regimen, if not to cost the patient. It is only after months and sometimes years of psychotherapy that a parent can accept such a formulation, so it behooves the pediatrician to exercise extreme caution and subtlety and a tangential approach in his discussions with the parents.

DR. JOSEPH K. CALVIN: Do babies that are overweight at about 1 year of age, say 28 to 30 pounds (12,700 to 13,608 Kg.), become more prone to develop obesity in preadolescence?

DR. GEORGE F. MUNNS, Winnetka: How often have you noticed that in the case of an obese child one or both of the parents are large bulky persons?

DR. MATTHEW M. STEINER (closing): Dr. Rosenstern has made some interesting comments on the "natural" course of preadolescent obesity. It is quite true, as was indicated earlier, that not all obese children require specific therapy. Whether such moderate obesity is the result of the emotional turmoil prior to puberty or associated with it or a part of the hormonal effects on fat deposit and fat distribution as androgen or estrogen increase, the fact remains that such children will outgrow their obesity with either a solution of their problems or maturation of their sex development. The problem with which we are concerned at present is the obesity that is an expression of some emotional disturbance and, as such, has been shown to persist beyond the age of adolescence and into adulthood.

Dr. Kerman is concerned with the attitudes of the parents toward this problem. It is essential to talk to parents in language they can grasp, in order to get their cooperation. There must be a good relation between the parents and the physician.

In answer to Dr. Calvin's question, I do not feel that because an infant is overweight before the age of 1 year the child will be obese later on. It is not a question of what the baby weighs at 1 year but of the factors in connection with the attitude toward food in the family and especially the attitude of the mother toward the child.

An Immunization Schedule for Children: A Plan for Simultaneous Prevention of Diphtheria, Tetanus and Pertussis. L. W. SAUER, Evanston, and W. H. TUCKER, Evanston (by invitation).

Because most deaths from pertussis occur during the first year of life and several months elapse before the development of active immunity from the injection of pertussis vaccine, immunization should be attempted as early as adequate and lasting protection can be attained.

Adequate immunity against diphtheria, tetanus and pertussis can be obtained simultaneously by administering three monthly doses of an alum-precipitated mixture of the three antigens to children over 6 months of age. For adequate protection before the sixth month, a monthly dose should be administered at the ages of 3, 4, 5 and 6 months. The following immunization schedule may be used:

Age, Mo.	Antigen *
3	Alum-precipitated d.t.p.
4	Alum-precipitated d.t.p.
5	Alum-precipitated d.t.p.
6	Alum-precipitated d.t.p.
7 †	Alum-precipitated d.t.p.
8	Alum-precipitated d.t.p.
9 to 12	Smallpox vaccination
2 to 3 yr. (before nursery school)	Booster dose, alum-precipitated d.t.p.
5 to 6 yr.	Booster dose, alum-precipitated d.t.p.; smallpox revaccination
At exposure or injury of previously immunized child	Prompt booster dose, fluid or alum-precipitated d.t.p.

* D. t. p. indicates diphtheria and tetanus toxoid and pertussis vaccine.
† If immunization starts at 3 months, the doses of antigen at 7 and 8 months are omitted.

Alternate gluteal areas are the most favorable sites for injection of alum-precipitated antigens. Delayed absorption increases the immunity response and lessens the severity of systemic reactions. The frequency of local reactions, such as alum cyst, is much decreased

by giving each dose deeply intramuscular with a ½ to ⅝ inch (1.3 to 1.6 cm.) needle (25 gage). Needles and syringes should be sterilized only by heat and a separate sterile needle used for each infant.

Reenforcing (booster) doses are recommended at 3 years and at 5 to 6 years of age, also after presumed exposure or after an injury. To help to protect infants against pertussis during the first nine months of life, previously immunized children under 12 years of age may be given a reenforcing (booster) dose if more than two years have elapsed since their last dose.

To decrease and ultimately eradicate pertussis morbidity and mortality, municipal and state health department bacteriologic diagnostic laboratories should be equipped to process cultures from cases of suspected pertussis. Diagnoses of diphtheria and pertussis should be made in the same laboratories. Private physicians, health department contagious disease physicians and nurses and infant welfare physicians and nurses should not only be pertussis minded but also be familiar with the nasopharyngeal swab method of taking cultures. Sterile nasopharyngeal swab, in labeled sterile glass tubes with explicit directions for impregnation, should be available. Earlier quarantine of pertussis patients and prompt isolation of exposed nonimmunes is a *sine qua non* in the prevention of epidemics.

Smallpox vaccination by the multiple pressure method on the left arm at the deltoid insertion is advisable in the spring or autumn after completion of the basic immunization. Scarlet fever and typhoid immunizations should be carried out when such protection is desirable. Smallpox revaccination should be performed when the child enters school at the age of 5 to 6, at the time that the booster dose of alum-precipitated diphtheria and tetanus toxoids and pertussis vaccine is administered.

DISCUSSION

DR. ARCHIBALD L. HOYNE: We have just heard an extremely interesting and instructive discussion. Drs. Sauer and Tucker have conducted a study of great importance. A day scarcely passes without someone wishing to know how early a child should be immunized. And in this respect the principal disease considered is pertussis. It seems to me that the schedule presented for immunizations is excellent. Some years ago, about 1940, the committee on immunization for Illinois of the American Academy of Pediatrics made certain recommendations which were published and distributed by the State Department of Health through the courtesy of Dr. Cross. At that time we advised 3 months as the age for inoculations against whooping cough and received some criticism for doing so. Our recommendation did not represent the unanimous opinion of the committee.

Dr. Sauer has been an intensive investigator in his well known studies of whooping cough and has established scientific facts in respect to immunization in early infancy. With regard to diphtheria the situation has changed. When this disease was prevalent, many people became immune as a result of subclinical infection. As a consequence, the newborn had often acquired from the mother a passive immunity which afforded protection for several months. With the marked decline in diphtheria, susceptibility is undoubtedly present much earlier in infancy than it was in the past, unless the mother has been artificially immunized. Therefore it is reasonable to inject diphtheria toxoid at the same time as pertussis vaccine.

Because smallpox can be contracted at any time after birth, very early vaccination may be indicated. Moreover, at one time it was suggested that a successful vaccination against smallpox diminished susceptibility to whooping cough. However, there is probably no foundation for such a belief, but every child should be vaccinated during the first year of life. In Cuba, according to information that has come to me, infants are vaccinated against smallpox and given their first injection of pertussis vaccine about 10 days after birth.

DR. WINSTON H. TUCKER, Evanston (closing): May I remind you that more infants die of pertussis or its complications than of all other communicable diseases combined. The largest number of deaths from pertussis occur in infants under the age of 6 months, and it is this group which is in greatest need of immunization against the disease.

Our immunization schedule represents 20 years of experience in pertussis immunization, during which time we have tested many different products, time intervals between injections, age at which immunization was attempted and routes of injection. We have settled on the alum-precipitated pertussis vaccine in combination with diphtheria toxoid or with diphtheria and tetanus toxoids. In order to achieve adequate basic immunity against pertussis, either

when pertussis vaccine is used singly or when it is used in combination with other antigens, each dose administered (whether 0.5 cc. or 1.0 cc.) should contain a minimum of 15,000,000,000 pertussis bacilli. We recommend that immunization against pertussis be started at 3 months of age and that a total of four consecutive injections be given at intervals of one month.

We have tried to immunize against pertussis infants as young as 2 weeks of age and found that in the age group up to 3 months of age antibodies against diphtheria and pertussis develop very poorly. Accordingly, we do not recommend that immunization be started in children younger than 3 months of age. We must bear in mind that immunity to communicable disease is relative and that it varies considerably in different persons. It therefore is essential that adequate basal immunity be achieved early in life, in order to compensate for the gradual drop in the antibody level as the child grows older. Stimulating (booster) doses should be administered at 3 and 5 years of age if the proper level of immunity is to be retained. As in all artificial immunization procedures, there will be a small percentage of failures, but pertussis immunization is now on a proved scientific basis and is a valuable preventive medical procedure that should be used routinely in medical practice.

DR. LOUIS W. SAUER, Evanston (closing): When you are doing health department immunizations you must be arbitrary. We have been conducting a clinic at the Evanston Health Department since 1931. Many of the babies are Negroes; the mothers are often forgetful. If more than two months intervene between any two doses we start all over. We have not found any hazard in doing this. When we first used alum-precipitated antigen, alum cyst

Basic Immunization Immunity Responses Three Months After Final Dose

			Diphtheria			Pertussis	
Age at Which Immunization Was Begun, Mo.	No. of Doses Received	No. of Patients	% Immune on Schick Test	% with 0.2 Unit or More Antitoxin/Ml. Serum	Tetanus % with 0.1 Unit or More Antitoxin/Ml. Serum	% with 3 or 4 plus Complement Fixation Reaction	% with Agglutination Reaction in Dilution of 1:320 or More
3	3	57	100	97	..	65	..
6	3	98	100	..	96	83	..
3	4	183	100	86	100	..	98

occurred on an average of once in 50 doses; with improvement in the technic of injection alum cyst occurred once in 800 doses; in 1949 there was no alum cyst.

In answer to the question on intradermal use of pertussis antigen I might say that years ago we attempted to immunize young infants that way. Three 0.1 cc. doses were injected intracutaneously in the tibia area for three successive weeks. Pertussis vaccine containing 10,000,000,000 bacilli per cubic centimeter was used. Three months after the final dose the complement fixation reaction showed little if any pertussis antibody. The average practitioner would find the intracutaneous administration of antigen too tedious; furthermore, it is quite painful unless the material reaches the subcutaneous layer. And in answer to the question on the best age to contract pertussis—I regret that I do not know.

We considered the agglutinogen skin test for pertussis immunity satisfactory; correlation with the complement fixation and agglutination tests was good. However, an allergist in New York considered the positive agglutinogen reaction an allergic (sensitivity) manifestation; an investigator in San Francisco found the test to give negative results in several immune children. As a result, the National Institute of Health has refused to release agglutinogen as a commercial skin test reagent. We now use the agglutination test for evidence of immunity to pertussis. However, if the latter is considered a reliable proof of immunity, the agglutinogen skin test seems equally reliable and simpler to perform.

Incidence of Mycotic Infections in Children with Acute Respiratory Tract Disease.
RALPH H. KUNSTADTER and ALBERT MILZER (by invitation).

A survey to determine the incidence of systemic mycotic infections in acute respiratory tract diseases was done on 211 children. On each child skin tests with various fungus antigens were done and a nasopharyngeal culture was made for pathogenic bacteria and fungi. Fungus

complement fixation tests as well as repeated bacterial and mycotic cultures of material obtained by gastric lavage, bronchial secretions and stools were carried out in selected cases in which there was pneumonic involvement.

No significant difference was found in the results of skin tests with histoplasmin, blastomycin, torulin or coccidioidin on children with pneumonia and acute upper respiratory tract infections and on the control group having no evidence of infectious disease. A total of 63 children with pneumonia were studied. Three were histoplasmin positive and tuberculin negative; one was histoplasmin positive and tuberculin positive; one was blastomycin positive only, and one was blastomycin and tuberculin positive. One was positive to Geotrichum filtrate only and one to Geotrichum filtrate and coccidioidin. Of the 72 children with upper respiratory tract infections, three were positive to histoplasmin only, three were positive to histoplasmin and tuberculin and one was positive to torulin only. In the control group of 76 children, three were histoplasmin positive only, four were positive to histoplasmin and tuberculin and one was positive to torulin only.

Three cases of proved fungus infection were demonstrated: (1) a case of primary histoplasmosis with clinical findings of atypical pneumonia in which Histoplasma capsulatum was isolated during the acute stage; (2) a case of fatal infection with granulomatous lesions of the lung, liver and kidney in which an unidentified fungus was isolated, and (3) a case of Candida albicans infection of the lung associated with malnutrition. Two cases of presumptive geotrichosis are described.

Although no significant correlation was found between systemic mycotic infections and acute respiratory tract disease in the present study, a fungus cause should be considered in cases of atypical pneumonia because of the positive findings described.

DISCUSSION

DR. ALBERT MILZER: The importance of employing multiple culture mediums in the isolation of pathogenic fungi must be emphasized. Mycologists no longer consider the inoculation of only Sabouraud's medium adequate but recommend the use of additional mediums such as Littman's, potato dextrose and cystine-brain-heart infusion agar containing 20 and 40 units per cubic centimeter respectively of penicillin and streptomycin. The antibiotics are added in order to inhibit growth of bacteria. It is also important to incubate duplicate cultures at both room temperature and 37 C. A thorough search for the tubercle bacillus must be made in suspected mycotic infections.

The value of the complement fixation test in diagnosis of mycotic infections has been discredited in the past. Recently, technics for performing these tests have been improved to the point that many workers feel that reliable results can now be obtained. There is some evidence in recent literature that antigens prepared from the yeast phase or polysaccharide fraction may be even more specific. A positive skin reaction may indicate a past or present infection. On the other hand, a positive complement fixation reaction is more likely to indicate an infection of recent origin.

Cross reactions between histoplasmin and blastomycin may occur in both skin and complement fixation tests, while coccidioidin is more specific. Usually the strongest positive reactions are obtained with the etiologic antigen. For this reason it is our practice at Michael Reese Hospital to run tests with all three fungus antigens simultaneously.

Mycotic as well as virusal and rickettsial infections must be considered in the etiology of the disease of patients with the clinical findings of atypical pneumonia. We have recently reported a proved, nonfatal case of primary histoplasmosis in a patient with atypical pneumonia. The multiplicity of antibiotic and therapeutic agents available today makes it imperative that a precise etiologic diagnosis be made so that the patient may obtain the full benefits of chemotherapy.

DR. RALPH H. KUNSTADTER (closing): I should like to make a few pertinent comments not brought out in the paper. Before treating certain systemic fungus infections with iodides, viz, blastomycosis, geotrichosis and moniliasis, in particular, it is important to desensitize with specific vaccine or antigen those patients who react positively to the specific intradermal test. Otherwise, an acute flare-up or progression of the disease may occur, as emphasized repeatedly by Conant and Smith.

The specificity of intradermal tests is frequently questioned. I believe it is generally agreed that there are no cross reactions among coccidioidin, tuberculin and other fungus antigens. However, there frequently occurs cross sensitivity between histoplasmin and blastomycin in the lower dilutions. Thus it is important to perform the various tests at the same time. In case the histoplasmin and blastomycin reactions are both positive (1 : 1,000 dilution), both tests should be repeated, since it has been demonstrated by Smith that the blastomycin reaction becomes negative in higher dilutions in the absence of blastomycotic infection. This is also true of the complement fixation reactions.

As in the case of the tuberculin test, the fungus skin tests give no information about how recent the infection is or whether an infection is healed, latent or recently active. Furthermore, in the case of histoplasmosis it may take several weeks before the skin test shows a positive reaction after initial infection. In overwhelming infections a previously positive reaction may become negative, indicating loss of immunity. Thus it is important to correlate the skin test with the complement fixation test, the reaction in the latter being negative in mild, inactive or healed infections and positive in severe infections and progressive disease.

In spite of the low incidence of systemic mycotic disease in acute upper respiratory tract infections and pneumonia in the Chicago area, nevertheless, such an etiologic possibility should be considered in all cases of so-called atypical pneumonia. We must realize that the diagnosis of primary atypical pneumonia is purely a clinical diagnosis and, in the majority of instances, no specific etiologic agent can be demonstrated. During the last war a committee on respiratory tract diseases, sponsored by the Surgeon General of the Army, studied many cases of primary atypical pneumonia in several military hospitals without establishing a specific virus as the etiologic agent. However, in sporadic cases of atypical pneumonia specific viruses such as those of lymphocytic choriomeningitis, lymphogranuloma venereum and psittacosis, have been demonstrated.

At Michael Reese Hospital Dr. Milzer and his associates are performing agglutination and complement fixation tests for identification of many of these viruses.

It is of interest that many of the early cases of primary coccidioidomycosis with acute upper respiratory tract symptoms and pulmonary infiitrates were diagnosed as primary atypical pneumonia before the true nature of the disease was established by Charles E. Smith. One of our cases of primary histoplasmosis was diagnosed as primary atypical pneumonia until H. capsulatum was recovered from the blood and bronchial secretions. Thus, it is our belief that a diagnosis of primary atypical pneumonia, cause undetermined, is justified only after a careful search for specific etiologic agents, namely, bacteria, viruses and fungi, has been made.

News and Comment

GENERAL NEWS

Specialists Certified by American Board of Pediatrics, Inc.—The following physicians were certified by the American Board of Pediatrics, Inc. after examinations in Boston on Dec. 1, 2 and 3, 1950:

Hyman Alford, Brookline Mass.; Lewis A. Barness, Warrington, Penn.; William Randal Bell, Marblehead, Mass.; Thomas Berry Brazelton, Cambridge, Mass.; William M. Browning, Indianapolis; Joseph R. Christian, Oak Park, Ill.; Gene Hofmeister Clarke, Buffalo; Charles Davenport Cook, Cambridge, Mass.; John J. Drucker, Forest Hills, N. Y.; Eileen Lanning Edelberg, Simsbury, Conn.; Paul G. Eglick, Philadelphia; Edmund Noyes Ervin, Waterville, Maine; John Gerard Flynn, Salem, Mass.; Francis H. Fox, Portland, Maine; Bennett Lewis Gemson, New Hyde Park, L. I., N. Y.; Philip Given Good, Portland, Maine; Leo F. Gowen, St. Louis; Summer Hagler, Quincy, Mass.; Albert E. Hensel Jr., Alexandria, La.; Harry Eugene Hile, Pittsburgh; John Platt Hubbell, Jr., Brookline, Mass.; John S. Hyde, River Forest, Ill.; David Mifflin Jones, Lafayette, Ind.; Stuart Lorin Joslin, Fairfield, Conn.; Hans George Keitel, Boston; Anna Katharine Kiehl, Walpole, Mass.; Barabara Maria Korsch, New York; Robert Lathrop Landraf, Niles, Mich.; Robert D. London, New York; Alexander S. MacDonald, Jr., Beverly, Mass.; Paul F. Maness, Burlington, N. C.; Robert James McKay, Burlington, Vt.; Russell Auger Morisette, Lewiston, Maine; Edna Zeltner Mortimer, Joliet, Ill.; Cornelius H. Nau, San Antonio, Texas; Robert J. Norton, Brooklyn; Michael Orange, Brooklyn; William David Penhale, Concord, N. H.; Harold Perkel, Bayonne, N. J.; M. Edwin Pesnel, Albany, N. Y.; William Peter Riley, Woodhaven, N. Y.; Albert Philip Rosen, Fair Lawn, N. J.; Alvin J. Schneider, Seattle; William C. Smith, Waynesboro, Va.; Gustav G. Steneck, Bogota, N. J.; John Wily Garret Tuthill, Weston, Mass.; Charles Orlan Tyler, Haddonfield, N. J.; George Robert Wade, Moorestown, N. J.; John Knox Wilson, Greensboro, N. C.; Paul Wilson, New York; Robert F. Wilson, Dover, N. H.; I. Robert Wood, Plattsburgh, N. Y.

ANNOUNCEMENTS

Society Meetings.—The next meeting of the Society for Pediatric Research will be held on May 2 and 3, 1951, at the Traymore Hotel, Atlantic City, N. J.

The National Society for Crippled Children and Adults, Inc., will hold its meeting in Chicago on Oct. 3, 4, 5 and 6, 1951.

Coming Examinations to be Held by American Board of Pediatrics, Inc.—Written examinations under local monitors will be held by the American Board of Pediatrics, Inc. on Friday, Jan. 19, 1951 from 2:00 to 4:00 p.m. This is the only written examination which will be given during 1951.

The next oral examination will be held in New Orleans on March 2, 3 and 4, 1951.

Pediatrics Postgraduate Seminar.—A series of seven Friday evening sessions on child care will be held at the Good Samaritan and the St. Joseph hospitals, Lexington, Ky., during February and March 1951. In addition to clinical case presentations there will be round table discussions. Physicians within a 75 mile radius will attend, and members of the American Academy of General Practice will receive 14 credit hours.

The program is planned for use in general practice and is presented by the Kentucky Child Health Foundation under the auspices of the University of Louisville School of Medicine. Members of their Pediatrics Department and the Lexington Fellows of the American Academy of Pediatrics will conduct the course, with Dr. Alex J. Steigman, Professor of Child Health, serving as chairman.

PERSONAL

Appointment of Dr. Bertram R. Girdany.—Dr. Bertram R. Girdany, formerly of Babies Hospital in New York, has joined the Pediatric Staff of Children's Hospital of Pittsburgh as physician in charge of the x-ray department. This appointment also carries teaching responsibilities in the Department of Pediatrics of the School of Medicine of the University of Pittsburgh. Dr. Girdany assumed his new position on Dec. 1, 1950.

Appointment for Dr. David Nye Barrows.—Dr. David Nye Barrows, director of gynecology and medical executive officer at the New York Polyclinic Medical School and Hospital, has been made dean of the institution as of Jan. 1, 1951. Dr. Barrows is also clinical professor of gynecology and obstetrics at New York University College of Medicine.

CORRECTION

In the abstract of "Serum-Anatoxin Therapy in Diphtheria, A. Visani, *Pediatria* **56**:193 (April) 1948," the first sentence should read "Ramon has recommended the following method of treating patients with diphtheria: the immediate injection of 0.1 cc. of diphtheria anatoxin (150 units per cubic centimeter); twenty minutes to one hour later the injection of diphtheria antitoxin in doses varying from 10,000 to 80,000 units according to the severity of the disease; forty-eight hours later an injection of 0.5 cc. of anatoxin, and at five day intervals further injections of 1, 2 and 3 cc. of anatoxin." In the abstract as it was published in the December issue of the AMERICAN JOURNAL OF DISEASES OF CHILDREN, page 1014, the clause beginning "twenty minutes to one hour" incorrectly contained the word "anatoxin" instead of "antitoxin."

SPECIAL NOTICE

For the general information of indexers, catalogers and library personnel with reference to the listing of the new title of this journal, we advise that the *Quarterly Cumulative Index Medicus* policy be followed. The *Quarterly Cumulative Index Medicus* with its volume 49 (January-June 1951) will list this journal under the new title, so that the letters A. M. A. will be included as an integral part of the title. For the completion of volume 48 (July-December 1950) the *Quarterly Cumulative Index Medicus* will continue to use the old title, without adding the designation A. M. A.

Book Reviews

Vision: Its Development in Infant and Child. By Arnold Gesell, M.D., Frances L. Ilg, M.D., and Glenna Bullis. Price, $6.50. Pp. 329, with 72 illustrations. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, 49 E. 33d St., New York 16, 1949.

Prior to this study of Gesell, Ilg and Bullis there have been remarkably few observations on the development of the visual functions in the infant and child and none of the comprehensive scope of this book. The material is well presented, beautifully illustrated and organized into the main headings termed "The Growing Action System," "Developmental Optics" and "Developmental Appraisal." Each subdivision is arranged chronologically according to the age of the child. In keeping with the authors' intention to consider vision in relation to the development of the child as a whole, much of the material, especially in the first half of the book, deals with nonvisual functions.

The subject should be of interest to pediatricians, ophthalmologists, psychiatrists, parents and teachers. The value put on the book will vary according to what one expects from it. The present reviewer, an ophthalmologist, found it disappointing. In it he noted inadequate standards of norms, an unsatisfactory bibliography, an unfamiliar vernacular and a plethora of generalizations with an insufficiency of statistically valid data. Especially unpalatable was the chapter on retinoscopy entitled "The Young Eye in Action," in which purely optical phenomena are endowed with psychic counterparts.

Admittedly a difficult subject, it is none the less important, and the authors could make a valuable contribution with their admirable perseverance and their kinographic technic for studying child behavior. It is to be hoped that their study of vision will be extended, preferably in conjunction with an ophthalmologist who is familiar with the pathologic aberrations and preferably with full use of such aids for investigating visual function as the opticokinetic response for measuring visual acuity and the bitemporal electrodes for recording eye movements. Such a study might be expected to give much needed information on the development of vestibular, reflex-visual and voluntary movements of the eyes, cycloplegic refraction of the eye at different ages and quantitative data on the development of visual acuity and color discrimination. So far as the authors have failed to provide such information the book falls far short of expectations.

Streptomycin und die Behandlung Haematogener Tuberkuloseformen. By Dr. Otto Ruziczka. Price, $4.80. Pp. 170, with 20 illustrations. Springer-Verlag OHG, Mölkerbastei 5, Wien I, 1949.

The monograph begins with a history of streptomycin, then its chemical formula is given, together with some general considerations. The production and the pharmacologic aspects are described, as well as directives for streptomycin treatment for tuberculosis and other diseases. To dosage, determination of streptomycin levels and the method of testing the sensitivity of tubercle bacilli to the drug, separate chapters are devoted. Chapters on the mechanism of its activity, its toxicity and hypersensitivity to the substance precede one describing experiments on tuberculous animals treated with streptomycin alone or in combination with sulfonamides. Streptomycin resistance is well discussed. The results reported from other countries with the treatment of miliary tuberculosis of the lungs and tuberculous meningitis are given. In the latter the additional intraspinal administration is outlined. These chapters make up 88 of the 179 pages. A number of the author's own patients with miliary tuberculosis, 11 in all, without meningitis, are reported on. The ages varied from 17 months to about 13½ years. The results were good. In other patients miliary tuberculosis of the lungs or other foci were associated with tuberculous meningitis. Of these patients, 50 in number, 18 (36 per cent) were dismissed as clinically healed, 18 (36 per cent) died and in 14

others treatment was not finished. These patients are discussed from various points of view in about 76 pages. The condition of 2 patients with peritoneal tuberculosis responded well to streptomycin therapy.

Morbo di Cooley: Clinica ed anatomia pathologica. By G. Maggioni and A. Ascenzi. Price, 1,200 lire. Pp. 168. G. Abruzzini, Via Levico 11, Rome, Italy, 1948.

Two cases of familial erythroblastic (Cooley's) anemia, 1 of a girl 27 months of age and the other of a boy 4 years old, are reported and form the basis of a critical review of the disease. The important clinical and pathologic contributions to the literature are abstracted, and the pathologic observations as reported for each organ and tissue are summarized and discussed. In a final chapter, thirty basic characteristics of the disease are listed. Three fundamental features of the disease are (1) myelosis, (2) pathologic involvement of bone and blood and (3) hemolysis.

The Emotional Climate of the Exceptional Child. Proceedings of the Spring Conference on Education and the Exceptional Child of the Child Research Clinic of the Woods School. No price given. Pp. 50. The Woods School, Langhorne, Pa., 1949.

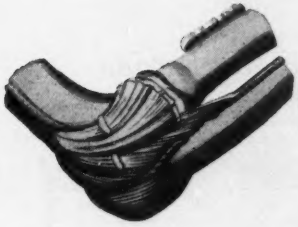
This pamphlet is a compilation of addresses presented at a Conference on Education and the Exceptional Child under the sponsorship of the Woods School Child Research Clinic. The subject of this conference was "The Emotional Climate of the Exceptional Child," Participants in the conference included many authorities in the fields of psychiatry, education and public health. The papers presented were entitled "The Social Group," "The Family," "The Church," "The Parents," "Medical Research" and "Community Planning." This wide variety of subjects indicates the great scope of these forty-eight pages. The original proceedings should be read by all who are interested in the problems of the exceptional child. Copies are obtainable from the Child Research Clinic, The Woods School, Langhorne, Pa.

Die Therapie der übertragbaren Kinderlähmung. By Dr. Kurt Hofmeier. Price, 7.50 marks. Pp. 112, with 6 illustrations and 4 tables. Georg Thieme Verlag, Diemershaldenstrasse 47, Stuttgart-O (American Zone), 1949.

The author objects to the publication of each case of poliomyelitis in the daily press. The main body of his book is devoted to the discussion of treatment. The first part describes some of the methods used at present. Reconvalescent serum may be administered on demand of the parents, although it is of no demonstrable effect on the course of the disease, nor does it possess any prophylactic value. Transfusion of whole blood may have a beneficial effect on the general condition, but a specific action is denied. Lumbar puncture, particularly when repeated, is not recommended. Treatment by drugs, including homeopathic treatment, may have a limited palliative effect on some symptoms. Physical therapeutic measures, such as diathermy or roentgen rays, are not recommended; the latter are directly condemned. Children with much pain of the spinal column may be treated with heat or cold. Electric stimulation of muscles may be omitted. With the "iron lung," the author has not sufficient experience of his own. Paralysis of deglutition and of mastication is discussed shortly. The results of the author's treatment of 160 patients are given, without claim of novelty. In the acute stage all patients suspected of paralysis are treated with hot packs one hour daily for six days. Furthermore, emptying of the bowels is stressed by such means as castor oil and enemas. Drugs are not employed regularly. Sister Kenny is credited with the emphasis on early active treatment in contradistinction to extensive immobilization. The main part of the therapy is active voluntary exercise, the various forms of which are discussed. The treatment should be conducted in collaboration with an orthopedic surgeon.

In the dictionary

"Joint" sometimes means...



"Joint" sometimes means...

On gamma globulin labels

(human)

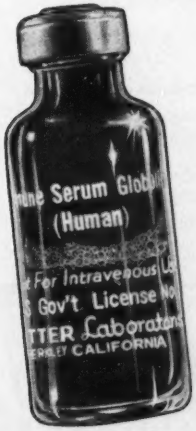
sometimes means

placental blood

(human) – CUTTER

always means

100% *venous* blood



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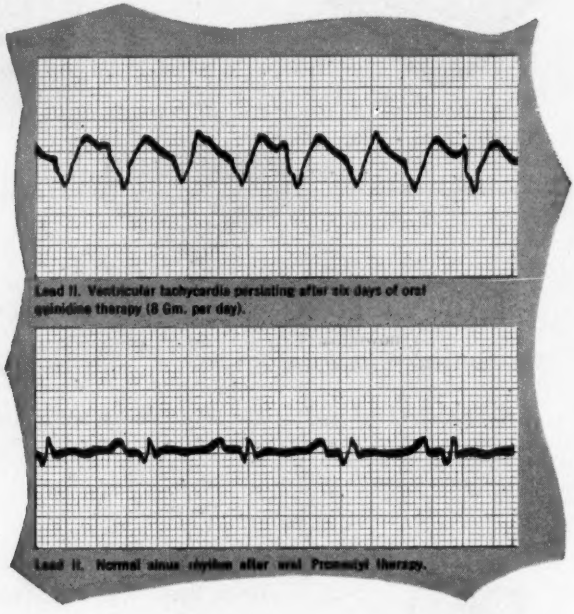

Lead II. Ventricular tachycardia persisting after six days of oral quinidine therapy (8 Gm. per day).

Lead II. Normal sinus rhythm after oral Pronestyl therapy.

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Fat	0.6 g
Phosphorus	180 mg
Iodine	10 mcg
Fluorine	1.5 mg
Choline	40 mg
Riboflavin	80 mcg
Niacin	12 mg
Animal Protein Factor (B_{12})	8 mcg per 100 grams
(94 calories per 100 grams, or 26.6 calories per ounce)	

ESSENTIAL AMINO ACIDS (Values given as percent of protein)	
Arginine	5.2
Histidine	5.7
Isoleucine	4.7
Leucine	7.0
Lysine	8.3
Methionine	2.8
Phenylalanine	3.5
Threonine	4.1
Tryptophan	1.1
Valine	5.2

VAN CAMP LABORATORIES

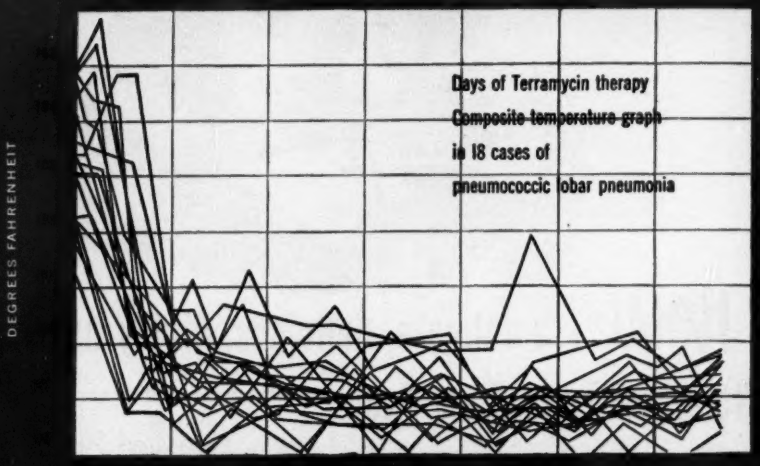
Division of Van Camp Sea Food Co., Inc.
Terminal Island, California

*Dunn, M. S.: The Nutritional Value of Fish Proteins, Institute of Food Technologists, San Francisco meeting, (July) 1949. Geiger, E.: Nutritive Value of Fish Protein, Progress in the Chemistry of Organic Natural Products, Ed. by L. Zechmeister, 5:275, 1948.

**McClure, F. J.: Fluorine in Foods, Public Health Reports, 64:1061, 1949.

A request on professional stationery to Dept. ADC will bring samples and bulletins.

PNEUMOCOCCIC LOBAR PNEUMONIA



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"With the exception of one subject... there was a dramatic fall in the temperature within twenty-four to thirty-six hours after the first dose of terramycin was given. The major decline in fever occurred during the first twenty-four hours after institution of therapy."

"Improvement in the acute symptoms... usually coincided with the fall in temperature. In many instances... symptomatic improvement actually preceded the fall in temperature."

Melcher, G. W.; Gibson, C. D.; Rose, H. M., and Kneeland, Y.: J. A. M. A. 143:1303 (Aug. 12) 1950.

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"Excellent" and "dramatic" response

"The response to terramycin therapy was considered excellent in every case and there were no cases in which treatment failed."

Melcher, G. W.; Gibson, C. D.; Rose, H. M., and Kneeland, Y.: J. A. M. A. 143:1303 (Aug. 12) 1950.

Dosage: On the basis of findings obtained in over 150 leading medical research centers, 2 Gm. daily by mouth in divided doses q. 6 h. is suggested for most acute infections.

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100 mg. capsules, bottles of 25 and 100;
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Terramycin may be highly effective even when other antibiotics fail.

Terramycin may be well tolerated even when other antibiotics are not.

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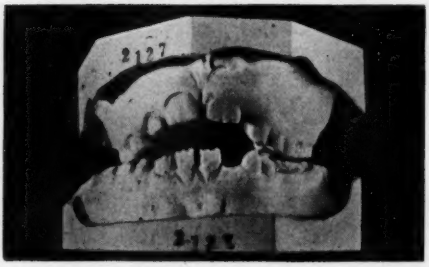
Four year old girl whose habit of putting fingers in mouth caused separation.

Same patient eight and one half years old. Habit was not broken. Permanent injuries have resulted, requiring orthodontic treatment.



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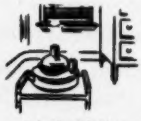

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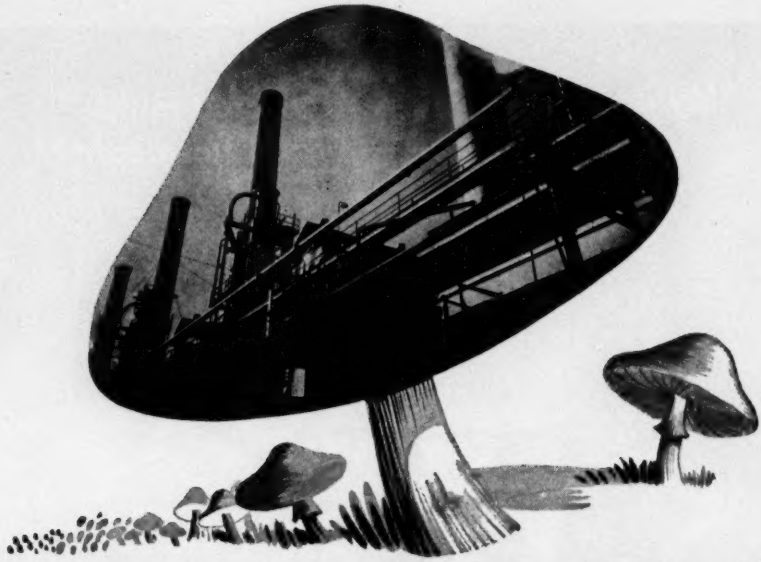

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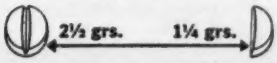

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---

(1) Mosenthal, H. O.: Management of Diabetes Mellitus: An Analysis of Present-Day Methods of Treatment, Ann. Int. Med., 29:79 (July) 1948.

(2) McLester, J. S.: Nutrition and Diet in Health and Disease, 5th ed., Phil., W. B. Saunders Company, 1949, page 364.

The Seal of Acceptance denotes that the nutritional statements made in this advertisement are acceptable to the Council on Foods and Nutrition of the American Medical Association.

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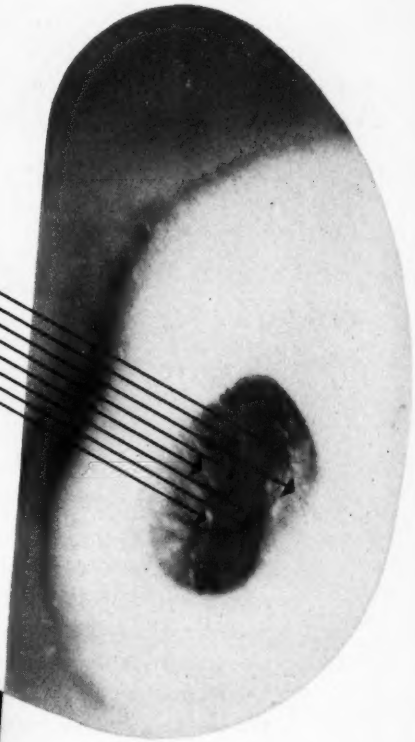
open

the nasal passages



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